Behavioral Phenotyping Neurofibromatosis Type 1

André B. Rietman

Behavioral Phenotyping Neurofibromatosis Type 1

Fenotypering van gedrag bij neurofibromatose type 1

André Bernard Rietman

* the daisy is the international symbol for Neurofibromatosis type 1

Colofon

The research in this thesis was financially supported by the Netherlands Organization for Health Research and Development (NWO- Zon Mw), Research Foundation Flanders (FWO-Vlaanderen), Sophia Foundation, KU Leuven 'Opening the future' fund, Marguerite-Marie Delacroix Foundation, Erasmus University, Fonds Nuts Ohra, and the Dutch Neurofibromatosis Association (NFVN).

Printing of this thesis was financially supported by the Dutch Neurofibromatosis Association (NFVN).

Cover Design: Philip Hopman and Katinka Krijgsman

Layout and printed by Proefschiftmaken|| www.proefschriftmaken.nl

ISBN: 978-94-6380-481-3

Behavioral Phenotyping Neurofibromatosis Type 1

Fenotypering van gedrag bij neurofibromatose type 1

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 2 oktober 2019 om 11:30 uur

door

André Bernard Rietman

geboren te Warnsveld, Nederland

Erasmus University Rotterdam

Promotiecommissie

Promotoren:	Prof. dr. Y. Elgersma
	Prof. dr. H.A. Moll
Overige leden:	Prof. dr. M.A. Grootenhuis
	Prof. dr. M.H.J. Hillegers
	Prof. dr. E. Legius
Copromotoren:	Dr. P.F.A. de Nijs
	Dr. M.C.Y. de Wit
Paranimfen:	Ron J. Rietman
	Jannemieke C. van Wolferen

When given the choice between being right and being kind, choose kind

Dr. Wayne W. Dyer

in R.J. Palacio's 'Wonder'

Table of contents

Manuscripts in this thesis

Chapter 2

Rietman AB, Oostenbrink R, Bongers S, et al. Motor problems in children with neurofibromatosis type 1. J Neurodev Disord 2017;9:19.

Chapter 3

Rietman AB, Oostenbrink R, van Noort K, et al. Development of emotional and behavioral problems in neurofibromatosis type 1 during young childhood. Am J Med Genet A 2017;173:2373-2380.

Chapter 4

Rietman AB, van der Vaart T, Plasschaert E, et al. Emotional and behavioral problems in children and adolescents with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2018;177:319-328.

Chapter 5

Rietman AB, Oostenbrink R, Plasschaert E, Descheemaeker MJ, de Wit MCY, ten Hoopen L, de Nijs PFA, Legius E, Moll HA. Predictors of mental quality of life of adolescents and young adults with neurofibromatosis type 1. Submitted 2019.

Chapter 6

van der Vaart T, Plasschaert E, Rietman AB, et al. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol 2013;12:1076-1083.

Chapter 7

van der Vaart T, Rietman AB, Plasschaert E, et al. Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:154-160.

Chapter 8

Rietman AB, van Helden H, Both PH, et al. Worries and needs of adults and parents of adults with neurofibromatosis type 1. Am J Med Genet A 2018;176:1150-1160.

CHAPTER 1.

General introduction
Aims and Outline

*The title of the drawing is ‘café-au-lait’;
so called ‘café-au-lait’-spots are a distinguishing feature of NF1

Alexander* *is a boy who is 14 years old when he comes to see the pediatrician and the pediatric neurologist of the outpatients' clinic for neurofibromatosis type 1 (NF1). Since he was 1 ½ years old, his parents and medical specialists thought he could have NF1, which was genetically confirmed when Alexander was six. Next to medical help in an academic hospital, he already had physical therapy, speech/language therapy, and psychological support. At the age of seven, psychological assessment points out he has average intelligence and a year later, autism with some characteristics of ADHD (attention-deficit/hyperactivity disorder) is being diagnosed at the psychiatry department of the hospital. A rehabilitation physician sees Alexander to treat his chronic complaints of fatigue and pain.*

Alexander comes with his parents to the NF1 Expertise Center of the Erasmus Medical Center (Erasmus MC) Sophia children's hospital because, in the other hospital, the specialists feel they do not have enough experience in dealing with NF1 in association with autism. In the neuropsychological evaluation, his limitations in processing speed, executive, and sensorimotor functions appear to affect his motivation, his activity level, and his all-over performance at school. To discuss these limitations and their impact on the daily life of Alexander and his family, Alexander and his parents see the psychologist of the expertise center for consultations every two months. Alexander is now 20 years old.

Merel* *is a 16-year-old girl who wants to join a psychosocial intervention she has heard of at a meeting of the NF1 patients' association. She knows she has NF1 since she was 12 years old, but apart from a plexiform neurofibroma (a painful bump on the back of her right arm) and some fatigue, she is quite happy and she does not experience any other complaints. She is curious to find out how other people experience NF1. When meeting other people with NF1, she thinks, "They all look rather normal, just like me." During the intervention, she learns that her motor 'clumsiness' could be seen as a part of NF1. Merel is capable of looking at NF1 from a distance, and in spite of her young age, some of her thoughts about NF1 are very striking and are being used in a brochure for young people with NF1. One of her quotes is, "I think it is hard to explain NF1 in one sentence. There are all kinds of things that go together with NF 1, like back pain and learning problems. You need an extensive story to explain all that. I feel like I fall in between everything, but there is no middle way."*

Alexander and Merel are two of the about 6000 people in the Netherlands having NF1. They are different in many ways: their age, sex, their jobs, the age at which they discovered they had NF1, and the extent to which NF1 is a burden for them. Since they both have NF1, it is also interesting to find similarities: They are both adolescents and they live with their parents, they both experienced problems in learning and they both experience more fatigue than their peers do.

*Names are fictitious, written informed consent obtained from persons involved

Background: The ENCORE expertise center

Since 2010, the Expertise Center for genetic neurocognitive developmental disorders Rotterdam Erasmus Medical Center ENCORE (Dutch acronym for *Erfelijke Neuro-Cognitieve Ontwikkelingsstoornissen Rotterdam Erasmus MC*: 'Genetic neurodevelopmental disorders Rotterdam Erasmus Medical Center') is combining the care for children with genetic disorders with both clinical and fundamental research. The outpatients' clinic for children with Neurofibromatosis type 1 was already present in the Erasmus MC Sophia Children's Hospital since 1985, mainly led by pediatrician Arja de Goede-Bolder and in 2012, it became part of the ENCORE expertise center for neurodevelopmental disorders that was founded by neuroscientist Ype Elgersma and pediatrician Henriette Moll. ENCORE is an effort to translate findings from research to care and daily life of persons with NF1, but also of other monogenetic neurocognitive (*neurogenetic*) disorders such as Tuberous Sclerosis Complex (TSC), Angelman syndrome, Fragile X syndrome, Sturge-Weber syndrome, Costello syndrome, and Cardio-Facio-Cutaneous syndrome (CFC). One of the aims of ENCORE is to contribute to the understanding of these syndromes, from a somatic, genetic, and psychological perspective. Since the start of ENCORE, a multidisciplinary team aims to help parents and patients in understanding their problems and in finding the right treatment for these patients.

From the start of ENCORE, one of the ways to optimize assessment of children with neurocognitive developmental disorders is the VOLG program (Dutch acronym for *Vroegtijdige Onderkenning Leer- en Gedragsproblemen*: 'Early recognition of problems in learning and behavior'). This program aims to standardize assessments of these children by neuropsychological and psychiatric assessments for all neurocognitive disorders on standardized ages, at 3, 6, 11, 15, and 18 years old. These are the ages at which, generally, decisions need to be made about the next step in education. This follow-up program facilitates longitudinal research aiming to reveal the natural history of learning and behavior in this population.

Follow-up is not the only way to ameliorate the understanding, assessment, and treatment of neurogenetic syndromes. Fundamental research and translating findings from this research to targeted treatment for cognitive and behavioral problems are important ways to provide insight in the underlying molecular, physiological, genetic, neurological, and psychological mechanisms of these syndromes. This translational research is an important part of the work of ENCORE[1-3]. The combination of multidisciplinary clinical practice with clinical and fundamental research has led to

the recognition by the Dutch federation of university hospitals (Nederlandse Federatie van Universitair Medische Centra: NFU) of ENCORE as a national expertise center in 2015.

Behavioral phenotyping in neurocognitive disorders

Genotype is described as the genetic make-up or code of cells or of an organism. Together with epigenetic factors and non-inherited environmental factors, it determines one's phenotype.[4] The phenotype (In ancient Greek, *φαίνω* (*phaino)* means 'to appear or to show', *τύποςs* (*typos)* means 'type') of an organism is the composite of the observable characteristics or traits, including morphology (physical form and structure), developmental processes, biochemical and physiological properties, and behavior.[5] A *behavioral phenotype* includes cognitive, personality, and behavioral patterns. Some behavioral phenotypes may characterize psychiatric disorders or syndromes. This more narrow definition of a behavioral phenotype is suggested to be "a behavior, including cognitive processes and social interaction style, that is consistently associated with, and specific to, a syndrome which has a chromosomal or genetic etiology ".[6] For patients with neurogenetic disorders and their parents, the diagnosis of a neurogenetic disorder itself is of limited use without a description of the somatic, cognitive, psychosocial, and behavioral features that usually accompany such a disorder. In neurogenetic disorders, some of these features are coined as '*endo-phenotypic'* characteristics or as *intermediate phenotype*. Endophenotypes are thought to be more easily quantifiable and more reliable than the clinical phenotype. This term is used in psychiatric genetics[7] in order to bridge the gap between behavioral symptoms and genetic characteristics.

In clinical assessment, treatment, and research of neurogenetic disorders, specialists cooperate in the somatic, the cognitive, and the psychosocial domains. The nature, severity and the natural history of somatic processes can have a large impact on cognitive and psychosocial processes. Neurocognitive and psychosocial assessments can provide a profile of strengths and weaknesses, a behavioral phenotype of the cognitive, sensory, motor, educational, behavioral, social, and emotional characteristics of patients[8].

Neurofibromatosis type 1 (NF1)

Neurofibromatosis type 1 (NF1) is a monogenic autosomal dominant neurodevelopmental disorder caused by heterozygous mutations in the *NF1* gene on chromosome 17q11.2.[9] This gene encodes for neurofibromin, a protein which is involved in modulating the rat-sarcoma (Ras) signaling pathway.[10] Possible mechanisms underlying learning and behavioral problems in NF1 are increased release of the inhibitory neurotransmitter GABA and impaired plasticity (LTP: long-term potentiation) in the hippocampus, as is shown in *Nf1*$^{+/-}$ mice [11-13].

Estimates of prevalence rates of NF1 vary between 1:2,052 (95% confidence interval (CI): 1:2,176 – 1:1,941)[14], 1:2,996 (95% CI 1:2,260 to 1:3,984),[15] and 1:4,560[16]. Estimates of the proportion of new (*de novo*) mutations in NF1 vary between 40% and 75%, leaving the other patients with familial or germline mutations.[16, 17] NF1 leads to symptoms such as *café-au-lait* macules, cutaneous, and subcutaneous neurofibromas but also to an increased susceptibility to various benign and malignant tumors. The major disease features of NF1 involve the nervous system, the skin, and the bones. Resulting complications are numerous, unpredictable, and vary even within families.[18] To enable and harmonize diagnostics, criteria were set by an NIH (National Institutes of Health) committee in 1987[19] (Table 1).

Diagnostic criteria for neurofibromatosis type 1 are met if two or more of the below criteria are found:
• Six or more café au lait macules (>0.5 cm in children or > 1.5 cm in adults)
• Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
• Freckling in axillary or inguinal regions
• Optic pathway glioma
• Two or more Lisch nodules (iris hamartomas seen on slit-lamp examination)
• Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/– pseudarthrosis)
• First-degree relative (parent, sibling or offspring) with NF1

Table 1. Diagnostic criteria for neurofibromatosis type 1

Café au lait patches and cutaneous neurofibromas occur in almost 100% of the cases and mainly have cosmetic effects. Subcutaneous and plexiform neurofibromas are less frequent (20-44%) and can lead to neurologic deficits and malignant change.[20] Plexiform neurofibromas[21] can cause neurological deficits and pain. Malignant peripheral nerve sheath tumors (MPNST) can occur from 5 years on and individuals with NF1 have a 7-13% lifetime risk of developing an MPNST.[18] MPNSTs and cardiovascular problems are the primary causes of an 8-15 years reduction in average life expectancy in both men and women with NF1.[22] Other frequent somatic symptoms are: macrocephaly (45%), small stature (below 25th percentile, 30%), scoliosis (10%), optic pathway glioma (15%), epilepsy (6-7%), precocious puberty (2-3%), and cerebral glioma (2-3%).[20]

The severity of NF1 is commonly scored by a physician who is specialized in NF1. The Riccardi scale is one of the instruments used to estimate NF1-severity.[23] In adults, sex and age do not seem

to be associated with NF1-severity, but there appears to be an association with general quality of life.[24] The Riccardi scale was also used in studies to find associations between severity of the somatic phenotype and the behavioral phenotype. To do this, the scale is modified by excluding cognitive or behavioral symptoms into the categories:

- Minimal NF1 (no features that compromise health, that is, only harmless cosmetic features such as café-au-lait maculae, freckling, and Lisch nodules),
- Mild NF1 (minor complications such as small stature or discrete plexiform neurofibroma),
- Moderate NF1 (complications that are a significant compromise to health, such as paravertebral neurofibromas or hypertension), and
- Severe NF1 (medical history with malignancy).[25]

Some studies found an association of severity of NF1 with didactic and neuropsychological tests in children.[25] NF1 is a progressive condition of which prognosis and cause are hard to predict. Some symptoms (café-au-lait spots, pseudarthrosis, and specific plexiform neurofibromas) are present in the first year of life. Mostly, freckling, optic gliomas, and scoliosis occur at school-age. MPNST's and some other plexiform neurofibromas generally occur in adulthood.[26] A relatively new factor is the information that comes to most people through the internet. When searching for NF1 with a web-browser, next to objective information, subjective and personal information and pictures of generally severely affected patients can be found by people of almost all ages. The unpredictable nature of NF1 and the impact of unfiltered information from the internet may have severe effects on the well-being of individuals with NF1. Although the diagnostic criteria are largely somatic and the physical symptoms are serious and impressive, cognitive deficits and behavioral problems are the most common complications of NF1 during childhood.[18, 27, 28]

Behavioral phenotyping of NF1

In the last decades, several reviews have described the behavioral phenotype of individuals with NF1.[29-32] With increasing knowledge, this gives a developing picture of the strengths and weaknesses on a diversity of domains: cognitive domains such as intelligence, language, visuospatial functioning, and executive function, behavioral domains such as emotional and social competence, and effects of NF1 on achievement and daily life.[32] As is the case with somatic symptoms, cognitive and behavioral profiles of children with NF1 are highly variable within and

between families. Below, the behavioral phenotype of NF1 is described from the perspectives of cognitive and behavioral problems and their effects on daily life.

Cognitive problems

In psychological assessment, intelligence is being used as a way to give an impression of general mental capabilities or cognitive abilities. The average full-scale intelligence quotient (IQ) of children with NF1 is lower than the IQ in the general population, in different studies varying from 86.2 (Standard deviation (*SD*) = 15.3) to 90.6 (*SD*= 13.3).[25, 28, 33, 34] In general, this indicates a left-shift of the normal distribution of 10 to 15 points (*SD* 0.6- 1.0). A left-shift is also visible when IQ scores of children with NF1 are compared with those of their siblings.[28, 34] Consequently, intellectual disability is twice as common in NF1 and there are more individuals with NF1 who have an IQ below 70 (6-8%, compared to 2% in the general population).[32, 33] Results regarding the intelligence profile mainly direct toward the conclusion that there is no significant difference between scores on verbal tasks and scores on performance tasks.[32] Figure 1 shows the distribution of intelligence scores measured with Wechsler scales in children aged 6-16 years old using density plots of total, verbal, and performance IQ scores.[35]

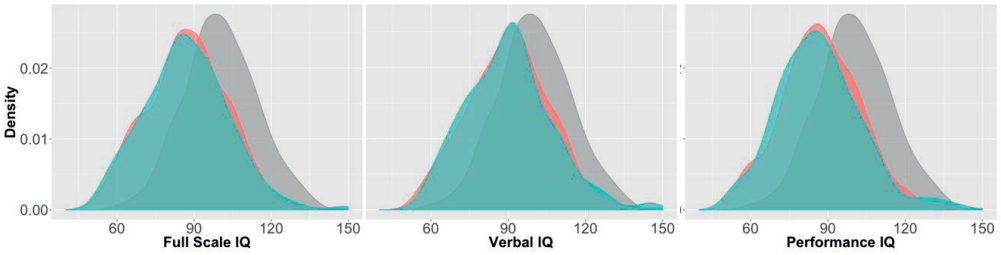


Figure 1. Distribution of intelligence scores in children with NF

(picture copied with the permission of the author: Myrthe Ottenhof)

Speech and language problems, such as delays in speech and language development, articulation disorders, have been found in toddlers, school-age children, and adults with NF1.[36, 37 38] These language abilities affect functional communication, social interaction, and social skills development. [37] Some authors look at language development in the light of general cognitive development and suggest that pure language-based learning disabilities are rare in NF1 and are

often part of a more general delay in development. Speech impairments seem to show a more distinctive profile in adults with NF1, with hypernasality and abnormal rate, volume, pitch, and articulation.[39, 40]

Since long, visuospatial and visuoconstructive deficits have been considered an important feature of the cognitive phenotype of NF1.[28, 32, 34, 41] Although scores on several instruments (RCFT: Rey Complex Figure Test and JLO: Judgment of Line Orientation) are below 1 SD compared to population means, some authors suggest these tests not only measure visuospatial functioning but also tap into executive functioning.[42, 43] Executive functions (EF) refer to a family of top-down mental processes facilitating the adaptation to novel situations: inhibition, working memory, and cognitive flexibility.[44] These functions are also affected in NF1 and are sometimes referred to as a core feature of the cognitive profile of children with NF1.[45] Different studies found deficiencies in EF, also after correcting for IQ.[46] Children with NF1 score lower than controls on tasks for cognitive flexibility, planning, and working memory.[46, 47] The association of scores on direct measures for EF with scores on measures for functional EF (i.e. the BRIEF, a parent-rated questionnaire for EF in daily life) is not always consistent.[48] Scores on the BRIEF mainly indicate problems in working memory, self-monitoring, and planning and organization.[48] A methodological problem is the use of a diversity of tests for different executive functions in different studies.[31, 49]

Attention (focused, sustained, or divided) as a construct overlaps with executive functioning[44] and seems to be one of the most consistently affected abilities in NF1, both when using direct measurements in neuropsychological assessments and when using indirect measures such as parental rating scales.[28, 48, 50] Attention problems are highly prevalent in NF1, although not all people with NF1 will meet the full criteria for ADHD.[51]

Motor problems may be affecting performance on tasks for executive function, visuospatial, or visual motor skills in NF1.[42] Both fine and gross motor skills are affected in 30-50% of children with NF1; [28, 42] almost 30 % of children with NF1 had had occupational therapy and over 40% had remedial teaching for these problems in school.[25]

Finally, studies focusing on memory problems in NF1 reported mixed results. Several studies did not find any selective memory problems.[1, 28, 52] Some small studies suggested problems in verbal memory but not in spatial memory[53] or in nonverbal memory.[54]

The distinction between cognitive and behavioral problems is arbitrary because many behavioral problems have cognitive aspects: Individuals with ADHD suffer from a lack of inhibition or other executive functions and problems in social interaction often occur due to deficits in social cognition. The most important emotional, behavioral, and social problems in NF1 are discussed below.

Behavioral problems

Behavioral problems in children are mainly assessed using parental rating scales. The majority of the problems found in NF1 concern emotional (also called 'internalizing') problems such as anxiety, depression, and social withdrawal. This may be associated with the social deficits and the self-image of individuals with NF1.[55] At preschool age, the amount of parent- and teacher-rated emotional and behavioral problems in NF1 is stable.[56] It is unclear what the natural history of these problems at school age is due to a lack of longitudinal studies. The most common behavioral disorder in NF1 is ADHD. In the general population, ADHD affects around 5% of the children and 2.5% of the adults.[57] The incidence of ADHD among children with NF1 is probably between 30 and 50%, although a formal diagnosis of ADHD is not always made in individuals with NF1 who do fulfill the criteria for ADHD.[28, 58-61] ADHD is more common in children with NF1 than in their siblings or their parents.[62] Interestingly, ADHD in NF1 seems to occur as frequently in boys as in girls, whereas the male: female ratio in the general population is 3:1.[28, 63]

Children with NF1 have poorer social outcomes than their siblings without NF1 have and they have significantly poorer social skills in comparison with normative data. They are frequently teased and rejected by their peers.[64] Children with NF1 and ADHD have the poorest social skills and social outcomes when compared to children with NF1 only or to children with NF1 and learning difficulties.[65] Severe social problems are observed in children with autism spectrum disorder (ASD). Although the estimated ASD prevalence in the general population is 0.8%, [66] ASD frequency estimates in children with NF1 range from 11 to 30%, depending on sampling method, country, and diagnostic instruments used.[63, 67, 68] Ideally, ASD classification is based not only on screening instruments but also on both observation scales and anamnestic information. Next to this, prevalence estimates must be based on large unselected groups of children with NF1. For this reason, the prevalence of ASD in NF1 is closer to 11 than to 30.[68] In addition, in a British population-based study an estimated 25% of the children met questionnaire criteria for both ADHD and ASD.[63]

Effects on daily life

Knowledge about the behavioral phenotype is mainly useful if this knowledge has a connection with the problems of individuals with NF1 in daily life. Making this connection is a way to validate this knowledge and the assessments that are necessary to acquire this knowledge. The World Health Organization (WHO) provides a framework for measuring health and disability. The International Classification of Functioning, Disability, and Health (ICF) is a classification of health and health-related domains in the context of an individual.[69] The ICF model is shown in Figure 2. In 2007, the WHO published the ICF for children and youth (ICF-CY).[70] The ICF is a framework that helps to identify the consequences of conditions such as NF1 not only in terms of functions and symptoms but also in terms of the effects in daily life. In this model, 'body functions and structures' refers to the different body systems and their specific roles. Activity is defined as the execution of a task or action or how an individual performs. Participation is defined as the involvement in a life situation or as what an individual does in daily life. In addition, the model includes contextual factors, referring to personal and environmental factors. Personal factors include features related to the individual, such as sex, age, education, fitness, coping abilities, and social and economic background. Environmental factors finally, concern physical, social, and attitudinal aspects of the environment of people that affect access to services, health benefits, opportunities, and information.[71]

Looking at the ICF model, it becomes clear that most of the above-cited research concerns effects of NF1 on the level of functions and activities, meaning there is a need to also describe effects of NF1 (and of limitations in functions and activities) on participation and to describe the interaction between these effects and contextual factors.

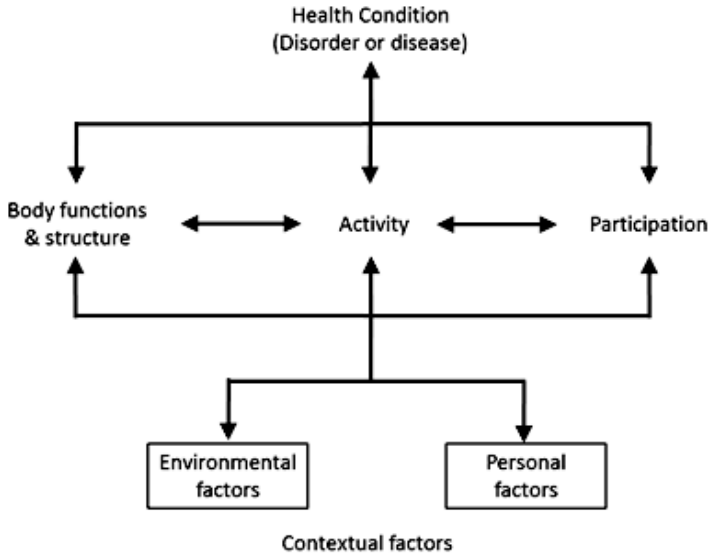


Figure 2. The WHO International Classification of Functioning, Disability, and Health (ICF)[69]

Many NF1-related complications (pain, anxiety, depression, cognitive issues, and organic sleep pathology) may interfere with sleep quality and cause sleep disturbance.[72] This is the case for both adults[72] and children.[58, 73] In children, the association with behavioral problems is inconclusive: one study found an association with conduct problems, hyperactivity, and emotional problems,[58] another did not find a relation with ADHD, cognitive impairment, nor stimulant medication use.[73] In children, sleep problems are associated with problems with school performance,[74] in adults, it is associated with unemployment status.[72]

One of the effects of cognitive and behavioral problems is the effect on academic skills and school performance. The majority of children (75%) perform one SD below their grade peers in spelling, mathematics, technical reading, or reading comprehension.[25] Visuospatial and motor problems can result in problems in handwriting, which are frequent in children with NF1.[28, 75] Children with NF1 repeat a grade in primary school significantly more often than children in the general population.[25, 76] Motor problems can limit participation at school and in play, sports, and peer-group activities, but they may also affect social and emotional development.[77] Most children with NF1 need additional support, for example, special education and/or remedial teaching.

On a systemic level, NF1 has its effects on relations, families, and communities. Children with NF1 have lower social competence, they have a reduced ability to get along with siblings, difficulties forming friendships and they have fewer friends.[64] Mothers of children with NF1 report higher levels of parental stress.[78] Possible reasons for this elevated stress are the emotional and behavioral problems of children but also difficulty coping with the uncertainty about the long-term prognosis of NF1.[79]

Only a few studies addressed participation in association with NF1. Children with NF1 were found to participate in a wide range of activities but showed an overall lower level of participation in activities compared to children from a normative sample with the lowest participation in skill-based and active physical activities.[64, 80]

Although patients with NF1 are at risk of significant clinical illness, most patients are only mildly affected and lead healthy and productive lives.[81] In spite of this, (health-related) quality of life (QoL) is lower for specific age groups in specific domains. In young children, parental perceptions of general health, growth, and development, and emotional impact were the most severely affected domains. Especially parental QoL scores about children with evident complications were very low, mainly in association with bodily pain.[82] Also in older children, adolescents, and in adults, QoL was found to be reduced across the majority of domains, both in proxy- and in self-ratings.[55, 83] Both visibility, specific symptoms and complications of NF1 and the variability and uncertainty about the course of NF1 seem to contribute to QoL.[84]

To summarize the areas of research and function in NF1 as a neurodevelopmental disorder using the ICF framework, Figure 3 shows the biological, somatic and functional domains where problems occur in NF1, where research is being conducted and where more research is needed. The icons of the eyes  at the top of the figure indicate the direction in which research attempts to connect domains:

1. The first eye from the left looks from Biology towards Tissue, Function, Activity, and Participation. This research, for instance, studies the effects of genotype on phenotype.
2. The second eye looks from Tissue towards Function, Activity, and Participation. This includes studies that look for the effects of somatic symptoms such as in Chapters 2 to 6.
3. The third eye looks from Function towards Activity and Participation. Almost all studies in this thesis also look for the associations between function/impairment and activity/disability
4. The fourth eye looks from Activity towards Participation. Mainly Chapters 5 to 8 contain studies that involve associations between activity/disability, participation, and quality of life. Instruments that measure the quality of life usually make a connection between activities and participation. For this reason, quality of life is not indicated in this figure.

		WHO International classification of function: ICF		
Biology [1]	**Tissue** [2]	**Function** [3]	**Activity** [4]	**Participation**
Cell	Peripheral nervous system	Cognition	Walking/running	Play
Nucleus	Central nervous system- Brain	Intelligence	Sitting	Work
Chromosome 17	Skin	Executive functions	Strenuous activities	School
NF1 Gene 17q11.2	Bones	Language	Driving a car	Social activities
Neurofibromin	Muscles	Motor coordination	Communication	Activities with family/parents
Ras-pathway	Circulation- Heart	Emotion regulation	Reading	Activities with friends
Neurotransmitters		Social skills	Writing	Sports and recreation
			Arithmetic	Music
Variations	**Symptoms**	**Impairment**	**Disability**	**Handicap**
Gene deletions	Café-au-lait macules	ADHD	Attention problems	Needing assistance at school
or mutations	Neurofibroma	ASD	Social problems	Dependent on support
	Plexiform Neurofibroma	DCD	Behavioral problems	Isolation/ loneliness
Decreased production	Glioma	Fatigue	Learning problems	Limited social network
or functionality of	Tumor growth	Intellectual disability	Decreased endurance	Conflicts
neurofibromin	Malignancy	Anxiety	Difficulties in planning/organizing	Inability to fully attend school/work
	Difficulties in	Mood disorders	Clumsiness	Inability to perform sports
Decreased production	Information processing	Difficulties in speech/language	Difficulties in communication	Limitations due to hospital visits,
or functionality of	Pain			therapy, medication, guidance/support
Neurotransmitters and	Itching			
other substances	Bone deformities			

[1]Effect of genotype on phenotype [2]Effect of somatic symptoms on function, etc. [3]Effect of function/impairment on activity, etc. [4]Effect of activity/disability on participation

Figure 3. Areas of research in NF1

Gaps in research of the behavioral phenotype in NF1

Since NF1 is a relatively rare disorder, many studies used small sample sizes, focused on a specific age group, and were performed in a selection of mainly Western societies (i.e. Western Europe, Australia, or North America). Studies to date vary widely in design, measures used, and participant groups. Consequently, generalizability over the NF1 population is often limited. Since clinical follow-up of NF1 patient-cohorts has become more common, research can focus on larger groups using data from multiple countries and cultures and broader age-groups. Because the majority of studies were observational cross-sectional studies, there is a need for more longitudinal studies that provide insight into the natural history of NF1 in both children, adolescents, and adults.

Another problem in the assessment of the behavioral phenotype is the wide variety of instruments used to measure specific cognitive and behavioral problems in NF1. For instance, motor proficiency can be assessed using tests targeting only parts of the motor domain and therefore do not show the full range of motor problems in children with NF1.[32] Broader test batteries for both fine and gross motor skills were only used in a limited number of smaller studies.[60, 85] For this reason, there is a need for studies that use broader test batteries measuring broad concepts such as cognition, behavioral problems, and motor proficiency.

Also, the selection of outcome measures in studies leads to distinct limitations. For instance, to measure emotional or behavioral problems in children with NF1, rating scales are often completed by proxies, e.g. parents and teachers, without taking the view of children or adolescents themselves into account.[29, 52, 65] Using self-rating scales as well could be an important contribution to the current knowledge about these emotional and behavioral problems. Next to this, selecting direct outcome measures (i.e. neuropsychological tests or observation) versus indirect measures (rating scales) has an effect on the outcome of a study and can yield different views and different conclusions, as is the case when comparing the direct neuropsychological assessment of executive functions with the outcome of parental ratings of executive functions.[48] Several studies in this thesis use information from multiple sources: ratings from parents, teachers, patients themselves or they use both indirect and direct outcomes.

Aims

This thesis aims to supplement the above gaps and to contribute to the knowledge about NF1 on cognitive, behavioral, emotional, and social domains of the behavioral phenotype and on the effects of this phenotype on daily life. The results of these studies can guide the direction of future follow-up programs, inspire future assessment and treatments, and improve intervention trials. Next to this, an intervention study targeting cognitive deficits and daily life functioning studies the efficacy and safety of simvastatin treatment. The overall aim is to improve the care for and the quality of life of individuals with NF1.

Outline

In the first chapters, knowledge about the behavioral phenotype is expanded with regard to motor, emotional, behavioral, and cognitive problems, fatigue, and participation. Knowledge about the behavioral phenotype is applied in the design of three studies, the SPOT study, the SIMCODA study, and a qualitative study regarding worries and care needs.

- **Chapter 2** focuses on the prevalence and severity of motor problems of children with NF1 and possible predictors.
- **Chapter 3** is a longitudinal study about the development of emotional and behavioral problems of young children with NF1 in association with their intellectual and language development.
- **Chapter 4** describes a cross-sectional study, defining the emotional and behavioral problems of a large group of children and adolescents with NF1.
- **Chapter 5** focuses on finding predictors for mental quality of life of adolescents and young adults with NF1 using the baseline measurement of the SPOT NF1 study (Dutch acronym for 'Social and Psychological support Of people with NF1 in their Teens or twenties').
- **Chapter 6** is an intervention study: the translational randomized placebo-controlled NF1-SIMCODA-trial (Simvastatin for cognitive deficits and daily life functioning), an RCT that studied the efficacy and safety of simvastatin treatment in a group of school-aged children and adolescents with NF1.
- **Chapter 7** evaluates the cognitive and behavioral outcome measures used in the SIMCODA trial in order to find how appropriate the selection of these measures was.

- **Chapter 8** studies the worries in daily life and the needs for care of adults with NF1 using a qualitative design**.**

This thesis is concluded with a **discussion**, summarizing and combining the findings, but also formulating implications and recommendations for future follow-up, treatment, and research.

References

1. Krab LC, de Goede-Bolder A, Aarsen FK, et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008;300:287-294.

2. van der Vaart T, Plasschaert E, Rietman AB, et al. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol 2013;12:1076-1083.

3. Overwater IE, Rietman AB, Bindels-de Heus K, et al. Sirolimus for epilepsy in children with tuberous sclerosis complex: A randomized controlled trial. Neurology 2016;87:1011-1018.

4. Wikipedia. Genotype [online]. Available at: https://en.wikipedia.org/wiki/Genotype. Accessed December 29.

5. Wikipedia. Phenotype [online]. Available at: https://en.wikipedia.org/wiki/Phenotype. Accessed December 2019.

6. Flint J. Annotation: behavioural phenotypes: a window onto the biology of behaviour. J Child Psychol Psychiatry 1996;37:355-367.

7. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636-645.

8. Riccio CAaR, C.R. Principles of Neuropsychological Assessment in Children and Adolescents [online]. Available at: http://www.oxfordhandbooks.com/view/10.1093/oxfordhb/9780199796304.001.0001/oxfordhb-9780199796304-e-014.

9. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999;89:1-6.

10. Martin GA, Viskochil D, Bollag G, et al. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. Cell 1990;63:843-849.

11. Cui Y, Costa RM, Murphy GG, et al. Neurofibromin regulation of ERK signaling modulates GABA release and learning. Cell 2008;135:549-560.

12. Costa RM, Federov NB, Kogan JH, et al. Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. Nature 2002;415:526-530.

13. Omrani A, van der Vaart T, Mientjes E, et al. HCN channels are a novel therapeutic target for cognitive dysfunction in Neurofibromatosis type 1. Mol Psychiatry 2015;20:1311-1321.

14. Kallionpaa RA, Uusitalo E, Leppavirta J, Poyhonen M, Peltonen S, Peltonen J. Prevalence of neurofibromatosis type 1 in the Finnish population. Genet Med 2018;20:1082-1086.

15. Lammert M, Friedman JM, Kluwe L, Mautner VF. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol 2005;141:71-74.

16. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

17. van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet 2014;85:318-327.

18. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol 2007;6:340-351.

19. NIH nioh. Neurofibromatosis. NIH Consens Statement 1987 Jul 13-15. 1987;6:1-19.

20. Ferner EF HS, Evans DGR. Neurofibromatosis in clinical practice. London: Springer-Verlag, 2011.

21. Mautner VF, Asuagbor FA, Dombi E, et al. Assessment of benign tumor burden by whole-body MRI in patients with neurofibromatosis 1. Neuro Oncol 2008;10:593-598.

22. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2018;20:671-682.

23. Riccardi V. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis., 2nd ed. ed. Baltimore, MD: Johns Hopkins University Press, 1992.

24. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421-1425.

25. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008;23:1002-1010.

26. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. Semin Pediatr Neurol 2006;13:2-7.

27. North KN, Riccardi V, Samango-Sprouse C, et al. Cognitive function and academic performance in neurofibromatosis. 1: consensus statement from the NF1 Cognitive Disorders Task Force. Neurology 1997;48:1121-1127.

28. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005;65:1037-1044.

29. Dilts CV, Carey JC, Kircher JC, et al. Children and adolescents with neurofibromatosis 1: a behavioral phenotype. J Dev Behav Pediatr 1996;17:229-239.

30. Kayl AE, Moore BD, 3rd. Behavioral phenotype of neurofibromatosis, type 1. Ment Retard Dev Disabil Res Rev 2000;6:117-124.

31. Ozonoff S. Cognitive impairment in neurofibromatosis type 1. Am J Med Genet 1999;89:45-52.

32. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

33. Ferner RE, Hughes RA, Weinman J. Intellectual impairment in neurofibromatosis 1. J Neurol Sci 1996;138:125-133.

34. Hyman SL, Arthur Shores E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Dev Med Child Neurol 2006;48:973-977.

35. Ottenhoff MJ, Rietman AB, Mous SE, Plasschaert E, Gawehns, Brems H, Oostenbrink R, ENCORE-NF1 center, van Minkelen R, Nellist M, Schorry E, Legius E, Moll HA, Elgersma Y. Examination of the factors underlying the cognitive variability associated with NF1. Submitted 2019.

36. Abdulian MH, Liu RW, Son-Hing JP, Thompson GH, Armstrong DG. Double rib penetration of the spinal canal in a patient with neurofibromatosis. J Pediatr Orthop 2011;31:6-10.

37. Brei NG, Klein-Tasman BP, Schwarz GN, Casnar CL. Language in young children with neurofibromatosis-1: relations to functional communication, attention, and social functioning. Res Dev Disabil 2014;35:2495-2504.

38. Lorenzo J, Barton B, Acosta MT, North K. Mental, motor, and language development of toddlers with neurofibromatosis type 1. J Pediatr 2011;158:660-665.

39. M. Lorch RF, J. Golding, R. Whurr. The nature of speech and language impairment in adults with neurofibromatosis 1. Journal of neurolinguistics 1999;12:157-165.

40. Alivuotila L, Hakokari J, Visnapuu V, et al. Speech characteristics in neurofibromatosis type 1. Am J Med Genet A 2010;152A:42-51.

41. Eliason MJ. Neurofibromatosis: implications for learning and behavior. J Dev Behav Pediatr 1986;7:175-179.

42. Levine TM, Materek A, Abel J, O'Donnell M, Cutting LE. Cognitive profile of neurofibromatosis type 1. Semin Pediatr Neurol 2006;13:8-20.

43. Plasschaert E, Van Eylen L, Descheemaeker MJ, Noens I, Legius E, Steyaert J. Executive functioning deficits in children with neurofibromatosis type 1: The influence of intellectual and social functioning. Am J Med Genet B Neuropsychiatr Genet 2016;171B:348-362.

44. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135-168.

45. Beaussart ML, Barbarot S, Mauger C, Roy A. Systematic Review and Meta-analysis of Executive Functions in Preschool and School-Age Children With Neurofibromatosis Type 1. J Int Neuropsychol Soc 2018;24:977-994.

46. Roy A, Roulin JL, Charbonnier V, et al. Executive dysfunction in children with neurofibromatosis type 1: a study of action planning. J Int Neuropsychol Soc 2010;16:1056-1063.

47. Ullrich NJ, Ayr L, Leaffer E, Irons MB, Rey-Casserly C. Pilot study of a novel computerized task to assess spatial learning in children and adolescents with neurofibromatosis type 1. J Child Neurol 2010;25:1195-1202.

48. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. Child Neuropsychol 2011;17:313-329.

49. Templer AK, Titus JB, Gutmann DH. A neuropsychological perspective on attention problems in neurofibromatosis type 1. J Atten Disord 2013;17:489-496.

50. Huijbregts S, Swaab H, de Sonneville L. Cognitive and motor control in neurofibromatosis type I: influence of maturation and hyperactivity-inattention. Dev Neuropsychol 2010;35:737-751.

51. Lion-Francois L, Herbillon V, Peyric E, et al. Attention and Executive Disorders in Neurofibromatosis 1: Comparison Between NF1 With ADHD Symptomatology (NF1 + ADHD) and ADHD Per Se. J Atten Disord 2017:1087054717707579.

52. Descheemaeker MJ, Ghesquiere P, Symons H, Fryns JP, Legius E. Behavioural, academic and neuropsychological profile of normally gifted Neurofibromatosis type 1 children. J Intellect Disabil Res 2005;49:33-46.

53. Billingsley RL, Slopis JM, Swank PR, Jackson EF, Moore BD, 3rd. Cortical morphology associated with language function in neurofibromatosis, type I. Brain Lang 2003;85:125-139.

54. Bawden H, Dooley J, Buckley D, et al. MRI and nonverbal cognitive deficits in children with neurofibromatosis 1. J Clin Exp Neuropsychol 1996;18:784-792.

55. Cipolletta S, Spina G, Spoto A. Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 12017.

56. Lorenzo J, Barton B, Arnold SS, North KN. Developmental trajectories of young children with neurofibromatosis type 1: a longitudinal study from 21 to 40 months of age. J Pediatr 2015;166:1006-1012 e1001.

57. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers 2015;1:15020.

58. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. Dev Med Child Neurol 2005;47:237-242.

59. Hendriksen JG, Peijnenborgh JC, Aldenkamp AP, Vles JS. Diagnostic overshadowing in a population of children with neurological disabilities: A cross sectional descriptive study on acquired ADHD. Eur J Paediatr Neurol 2015;19:521-524.

60. Hofman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: the cognitive phenotype. J Pediatr 1994;124:S1-8.

61. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Dev Med Child Neurol 2002;44:164-170.

62. Koth CW, Cutting LE, Denckla MB. The association of neurofibromatosis type 1 and attention deficit hyperactivity disorder. Child Neuropsychol 2000;6:185-194.

63. Garg S, Lehtonen A, Huson SM, et al. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. Dev Med Child Neurol 2013;55:139-145.

64. Johnson NS, Saal HM, Lovell AM, Schorry EK. Social and emotional problems in children with neurofibromatosis type 1: evidence and proposed interventions. J Pediatr 1999;134:767-772.

65. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-563.

66. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychological Medicine 2015;45:601-613.

67. Plasschaert E, Descheemaeker MJ, Van Eylen L, Noens I, Steyaert J, Legius E. Prevalence of autism spectrum disorder symptoms in children with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2014.

68. Eijk S, Mous SE, Dieleman GC, et al. Autism Spectrum Disorder in an Unselected Cohort of Children with Neurofibromatosis Type 1 (NF1). J Autism Dev Disord 2018;48:2278-2285.

69. WHO WHO. International Classification of Functioning, Disability and Health (ICF) [online]. Available at: https://www.who.int/classifications/icf/en/. Accessed 23-01-2019.

70. WHO WHO. International classification of functioning, disability and health: children & youth version: ICF-CY2007.

71. Gilboa Y, Rosenblum S, Fattal-Valevski A, Josman N. Application of the International Classification of Functioning, Disability and Health in children with neurofibromatosis type 1: a review. Dev Med Child Neurol 2010;52:612-619.

72. Leschziner GD, Golding JF, Ferner RE. Sleep disturbance as part of the neurofibromatosis type 1 phenotype in adults. Am J Med Genet A 2013;161A:1319-1322.

73. Licis AK, Vallorani A, Gao F, et al. Prevalence of Sleep Disturbances in Children With Neurofibromatosis Type 1. J Child Neurol 2013;28:1400-1405.

74. Astill RG, Van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol Bull 2012;138:1109-1138.

75. Gilboa Y, Josman N, Fattal-Valevski A, Toledano-Alhadef H, Rosenblum S. The handwriting performance of children with NF1. Res Dev Disabil 2010;31:929-935.

76. Coude FX, Mignot C, Lyonnet S, Munnich A. Early grade repetition and inattention associated with neurofibromatosis type 1. J Atten Disord 2007;11:101-105.

77. Skinner RA, Piek JP. Psychosocial implications of poor motor coordination in children and adolescents. Hum Mov Sci 2001;20:73-94.

78. Esposito M, Marotta R, Roccella M, et al. Pediatric neurofibromatosis 1 and parental stress: a multicenter study. Neuropsychiatr Dis Treat 2014;10:141-146.

79. Martin S, Struemph KL, Poblete A, et al. An Internet support group for parents of children with neurofibromatosis type 1: a qualitative analysis. J Community Genet 2018;9:327-334.

80. Johnson BA, Sheng X, Perry AS, Stevenson DA. Activity and participation in children with neurofibromatosis type 1. Res Dev Disabil 2015;36C:213-221.

81. North K. Neurofibromatosis type 1. Am J Med Genet 2000;97:119-127.

82. Oostenbrink R, Spong K, de Goede-Bolder A, Landgraf JM, Raat H, Moll HA. Parental reports of health-related quality of life in young children with neurofibromatosis type 1: influence of condition specific determinants. J Pediatr 2007;151:182-186, 186 e181-182.

83. Vranceanu AM, Merker VL, Park E, Plotkin SR. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: a systematic review of the literature. J Neurooncol 2013;114:257-262.

84. Draucker CB, Nutakki K, Varni JW, Swigonski NL. The health-related quality of life of children, adolescents, and young adults with neurofibromatosis type 1 and their families: Analysis of narratives. J Spec Pediatr Nurs 2017;22.

85. Johnson BA, MacWilliams BA, Carey JC, Viskochil DH, D'Astous JL, Stevenson DA. Motor proficiency in children with neurofibromatosis type 1. Pediatr Phys Ther 2010;22:344-348.

CHAPTER 2.

Motor problems in children with neurofibromatosis type 1

Rietman AB, Oostenbrink R, Bongers S, Gaukema E, van Abeelen S, Hendriksen JG, Looman CWN, de Nijs PFA, de Wit MCY

Journal of Neurodevelopmental Disorders 2017;9:19

Abstract

Background and aim

Children with the neurogenetic disorder neurofibromatosis type 1 (NF1) often have problems with learning and behaviour. In both parent reports and neuropsychological assessment, motor problems are reported in approximately one-third to one-half of the children with NF1 [1-3]. Studies using broad motor performance test batteries with relatively large groups of children with NF1 are limited. The aim of this cross-sectional observational study was to describe the severity of motor problems in children with NF1 and to explore the predictive value of demographics, intelligence, and behavioural problems.

Methods

From 2002 to 2014, 69 children with NF1, aged 4 to 16 years (age = 9.5 $\pm$ 2.8 years; 29 girls) had a motor, psychological, and neurological evaluation in an NF1 expertise centre. Data were collected about (1) motor performance (M-ABC: Movement Assessment Battery for Children), (2) intelligence, and (3) emotional and behavioural problems as rated by parents.

Results

Sixty-one percent of these children scored within the clinical range of the M-ABC. In ordinal logistic regression analyses, motor problems were associated with symptoms of Attention-Deficit/ Hyperactivity Disorder (ADHD), symptoms of Autism Spectrum Disorder (ASD), and externalising behavioural problems. Motor outcome was not predicted by age, intelligence, scoliosis, hypotonia, nor hypermobility.

Conclusions

Motor problems are among the most common comorbid developmental problems in children with NF1 and these problems do not diminish with age. Because of their impact on daily functioning, motor problems need to be specifically addressed in diagnosis, follow up and treatment of NF1.

Background

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurogenetic disorder with an incidence of at least 1:2,700.[4] Although NF1 is defined by cutaneous and neurological symptoms such as café-au-lait spots and neurofibromas, the most common complications in childhood are deficits of cognition and of social and emotional development.[5] The prevalence of neuropsychiatric problems such as Attention-Deficit/ Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) is much larger than in the general population.[6] In both parent reports and neuropsychological assessments, motor problems are reported in approximately one-third to one-half of the children with NF1. [2, 3] Almost 30% of children with NF1 had received occupational therapy [1] and over 40% receive remedial teaching for motor problems at school.[7] NF1 related skeletal and muscular abnormalities, such as scoliosis, pseudo-arthrosis, decreased bone strength, and reduced muscle strength may be associated with motor problems in NF1.[3] Motor problems can hinder a child's participation at school, and in play, sports, and peer-group activities but they may also affect social and emotional development[8]. In our expertise centres for NF1, motor problems are amongst the most common complaints, which is the reason for the structural assessment of motor skills presented in this study.

Previous studies on motor skills in NF1 have often used selective tests, targeting only parts of the motor domain.[5, 9] Studies using a small selection of motor or constructional tests do not show the full range of motor problems in children with NF1. Broader test batteries for both fine and gross motor skills have been used in a limited number of smaller studies [3, 10] or when focusing on young children.[2, 11] Recently,[9] a broad test battery (the BOT-2) was used with 46 children, from 7 to 17 years old, to establish correlations between problems in motor and cognitive domains. In this study, cognition was associated with balance, gait, running speed and agility in children with NF1. A shared abnormal neurodevelopmental process underlying cognitive and motor abilities in NF1 was hypothesized.[9]

A study on a large group of children and adolescents with NF1, using a broad test battery for motor performance, could inform health care professionals not only about the association between motor problems and cognitive development but also about the association with the emotional and behavioural problems often present in NF1. Our cross-sectional study aims to describe the presence and severity of motor problems in children and adolescents with

Neurofibromatosis type 1 (NF1) and to explore the associations between these motor problems and background variables, intelligence, and emotional and behavioural problems.

Methods

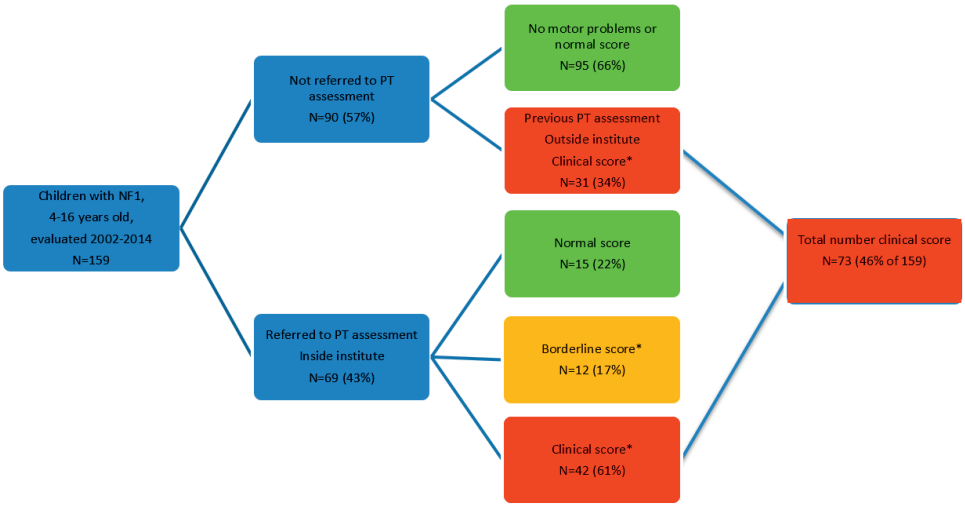
Procedure and Patients

The Kempenhaeghe Centre for Neurological Learning Disabilities (CNL) is an expertise centre for children with neurological learning disabilities such as NF1. At school age, a paediatric neurologist evaluates all patients at least once. Patients are offered additional evaluations by a neuropsychologist and a physiotherapist. Patients without any complaints about motor performance were not included in this study. Next to this, we did not re-evaluate the motor performance of patients who already had serious motor problems according to a recent evaluation by a physiotherapist using the Movement- ABC in a different institute. The selection process is depicted in Figure 1. We used medical and psychological patient files from 2002 to 2014 of 4 to 16 year old patients who met the National Institutes of Health (NIH) diagnostic criteria for NF1,[12] and who were evaluated by a physiotherapist using the Movement Assessment Battery for Children version 1[13] or 2[14] (M-ABC-1 or 2). Exclusion criteria were: segmental NF1, symptomatic pathology of the CNS, deafness or severely impaired vision, pseudarthrosis, insufficient command of the Dutch language, or an IQ below the range covered by the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL[15]; Total IQ below 48).

Clinical data were registered by a paediatrician of Erasmus Medical Centre, Sophia Children's Hospital during annual follow-up, by a paediatric neurologist from CNL, and by psychologists from both centres. All children were evaluated according to a standardized protocol, routinely applied to all children with NF1 visiting the expertise centre. Familial or sporadic NF1 was determined from family history. In clinical assessments by the paediatric neurologist and the psychologist, the presence of neurologic, orthopaedic or neuropsychiatric problems such as hypotonia, hypermobility, and scoliosis were recorded. Classifications of ADHD and ASD were based on neuropsychological assessment and on information from parents and teachers, using DSM-IV[16] criteria. Writing problems were reported by parents. Socio-economic status (SES) was derived from the zip code of the child's home address using a standard Dutch classification system

[17]. For the participating patients, a formal review and waiver was given by the medical ethical human research ethics committees of both the Erasmus Medical Centre and the CNL.

Figure 1. Flow chart of participants and outcomes



* M-ABC Normal score: > P15; Borderline score: P5 to < P15; Clinical score: < P5

Instruments

The Movement ABC,[13, 14] an instrument measuring the presence and severity of motor problems, is one of the most frequently and widely used standardized assessments of motor skills, also used in diagnosing DCD. To assess motor performance, the physiotherapist administered the M-ABC-1[13] (2002-2010) or 2[14] (2010-2014). The M-ABC assesses three components: manual dexterity, ball skills (catching and throwing), and balance (static and dynamic). The M-ABC is designed to identify and describe impairments in the motor performance of children and adolescents aged 4 to 12 (M-ABC-1) or 3 to 16 (M-ABC-2). The M-ABC-2 is an updated version of the M-ABC-1: not only the age range but also the sample size, have been expanded and more information on psychometric qualities has been acquired. Results on both tests are expressed in a

score, with any child scoring below the 6th percentile of the normative sample being recorded as falling within the clinical range indicating serious movement difficulties. Scores from the 6th to the 15th percentile (approximately between 1.5 and 2.0 SD below average) are labeled as borderline, indicating that the child is at risk of motor problems. Above the 15th percentile, the child is unlikely to have movement difficulties. Additionally, the M-ABC-2 also provides norm-referenced standardized scores for the component and the total scores. The M-ABC-2 has good reliability (ICC = .95 to .98).

Intelligence was measured with the Wechsler Preschool and Primary Scale of Intelligence-Revised, Dutch version (first WPPSI-R[18], from 2010 WPPSI-III-NL[19]) or the WISC-III-NL[15]. These are intelligence tests for children, the first for those aged 2 years and 6 months to 7 years and 7 months, and the second for children aged 6 to 17 years. The tests consist of several subtests resulting in a Full-Scale IQ, Verbal IQ, and Performance IQ.

To assess emotional and behavioural problems, parents completed the Child Behavior Checklist (CBCL) using either the preschool version, the CBCL/1½-5[20], or the school-aged version, CBCL/6-18[21]. Scores were converted to T scores (mean 50, *SD* 10), with higher scores corresponding to more problems. Summed scores result in three broad-band scales for Internalising, Externalising, and Total Problems. The Internalising Problems scale comprises anxious/depressed behaviour, withdrawn/depressed behaviour, and somatic complaints. The Externalising Problems scale comprises rule-breaking behaviour and aggressive behaviour. The Total problems scale is a combination of both the Internalising and Externalising Problems scales, together with scales for Social Problems, Thought Problems, and Attention Problems. T scores between 59 and 62 fall within a borderline clinical range, whilst T scores of 63 and higher fall within the clinical range. All tests were administered in their Dutch versions, using Dutch normative samples.

Statistical analysis

All data were analysed using SPSS, version 21[22], and R.[23] Proportions of groups were compared using chi-square (χ^2) tests. Effect sizes were calculated using Cohen's *d*,[24] when comparing the NF1 sample with the test manual normative sample, with .20 interpreted as a small effect size, .50 as medium, and .80 as large.

Since the common outcome for both versions of the M-ABC was the classification into three consecutive categories (normal, borderline, or clinical), ordinal logistic regression analysis

was performed to find predictors of these three categories of motor outcome. For this, a two-phase strategy was followed. In phase 1, all separate variables from Table 1 were tested in univariable ordinal regression analyses with M-ABC classification as the dependent variable. Since this phase served as an initial, broad selection of potential predictors, α in phase 1 was set at .20[25]. In phase 2, multivariable ordinal regression models were constructed for every block of variables from Tables 1 and 2, containing all significant variables from phase 1. Blocks were defined as demographics, neuropsychiatric problems, emotional and behavioural problems, and cognition. Variables shown to be significant contributors in the final models were regarded as the final predictors of M-ABC motor outcome (α in phase 2 was set at .05; stepwise backward elimination procedure).

Results

Patient characteristics

From 2002 to 2014, 159 children with NF1 aged 4 to 16 years old visited the expertise centre. Ninety (57% of 159; 46 girls and 44 boys) were not referred to the physiotherapist, of which 31 (34% of 90) had a previous assessment outside our institute, indicating serious motor problems, according to M-ABC-scores in the clinical range. Of the other 59 (66% of 90), parents and children did not have any complaints about motor performance before or during their visit to our institute. In the flow chart of Figure 1, we have visualized the distribution of the sample. For this study, 69 children (43% of 159) with NF1 were included for PT evaluation in our institute, 29 girls, and 40 boys. This group is indicated in the box 'Referred to PT assessment' in Figure 1. Ages ranged from 4 years to 15 years and 11 months, with a median age of 8 years and 8 months (IQR= 4y 1mo) (Table 1). Sixty-seven children were right-handed.

Table 1. Characteristics of children with NF1

Variable	*n* = 69
Demographic characteristics	Frequency (%)
Age	8.7 (4.1)[a]
Gender	
Male	40 (58)
Female	29 (42)
Type of education	
Regular education	48 (70)
Special education	21 (30)
Social Economic Status [b]	0.34 (1.29)[a]
Mode of inheritance NF1	
De novo mutation	39 (57)
Familial mutation	29 (42)
Unknown	1 (1)
Neuropsychiatric problems	
Attention-Deficit/ Hyperactivity Disorder (ADHD)	
ADHD combined type	25 (36)
ADHD inattentive type	11 (16)
ADHD hyperactive/impulsive type	2 (3)
Total	38 (55)
Using stimulant medication	18 (26)
Autism spectrum disorder (PDD-NOS)	7 (10)
Neurologic and orthopaedic problems	
Hypotonia	14 (20)
Hypermobility (Beighton criteria)	13 (19)
Scoliosis	7 (10)

[a] Median (interquartile range) [b]Average SES in 2010 = 0.17; higher scores indicate higher SES

Eighteen out of 38 of the children with a DSM-IV-TR classification of ADHD (47%) used stimulant medication. Seven children had an ASD classification, all of them with a comorbid ADHD classification. Intelligence, emotional and behavioural problems, and standard scores of the M-ABC-2 are presented in Table 2.

Twenty-four children (41%) had emotional and behavioural problems scores within the clinical range, with large effect sizes for internalising problems and medium effect sizes for externalising problems. Parents of 11 children (16%) did not return CBCLs. These children were left out of analyses using CBCL scores as predictors. Compared to the normative sample, the distribution of intelligence scores was shifted approximately one *SD* to the left, and total IQ scores ranged from 58 to 123. Effect sizes were large for performance IQ and medium for verbal IQ compared to the normative population. Effect sizes for all motor scales were large.

Motor problems

Thirty-five of 69 children (51%) were assessed with the M-ABC version 1, 34 (49%) with version 2. The comparison between children tested with these two versions showed no significant differences in the distribution of scores between the percentile classification categories for the total scores (χ^2 (2) = 3.08, p = .21), nor for distributions of Hand, Ball or Balance scale scores. For the purpose of ordinal regression analyses, both groups were combined. Figure 2 presents the distribution of the classifications in all motor scales. Overall, 42 (61%) children with NF1 scored within the clinical range (below 6th percentile) of the M-ABC.

In ordinal regression analysis, age was found not to be a significant predictor of motor outcome. The proportion of children scoring in the 'borderline' or 'clinical' range of the M-ABC was 67% of children from 4 to 6 years old, 82% of children from 7 to 11 years old, and 79% of adolescents from 12 to 16 years old.

In univariable ordinal regression analysis (Table 3; phase 1 with α set at .20), a higher probability of borderline or clinical motor problems was predicted by type of education, classifications of ADHD or ASD, hypermobility, Performance IQ, Total IQ, and CBCL Internalising, Externalising, and Total Problems. In all univariable models, the test of parallel lines failed to reach significance, meaning that effects of all separate variables were the same for normal versus borderline and borderline versus clinical scores.

Table 2. Scores and frequencies for emotional and behavioural problems, intelligence and motor performance

Domain	*Number*	*Mean*	*SD*[a]	*BCR*[b] *(%)*	*CR*[b] *(%)*	*ES*[c]
Parent-rated emotional and behavioural problems[d]						
Internalising problems	58	59	10	19	37	0.9***
Externalising problems	58	55	12	8	27	0.5**
Total problems	58	61	11	10	41	1.0***
Intelligence[e]						
Verbal IQ	68	92	15			0.5***
Performance IQ	68	88	14			0.8***
Total IQ	69	89	13			0.8***
Movement ABC-1 and 2 (*n*= 69)						
Classification Normal[f]	15 (22%)					
Classification Borderline[f]	12 (17%)					
Classification Clinical[f]	42 (61%)					
Movement ABC-2[g] (*n* = 34)						
Manual dexterity	34	5.8	3.3			1.3***
Ball skills	34	6.7	3.6			1.0***
Balance	33	5.7	3.0			1.4***
Total	34	4.8	3.2			1.7***

[a] SD = Standard Deviation [b] *BCR/CR*: Percentage of scores in borderline clinical range/clinical range

[c] ES: effect size (Cohen's d); Significance compared to normative sample $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$

[d] T scores (population mean = 50; SD = 10; higher scores reflect more problems)

[e] IQ scores (population mean = 100; SD = 15; higher scores reflect better performance)

[f] M-ABC Normal score: > P15; Borderline score: P5 to < P15; Clinical score: < P5)

[g] Standard-scores (population mean = 10; SD = 3; higher scores reflect better performance)

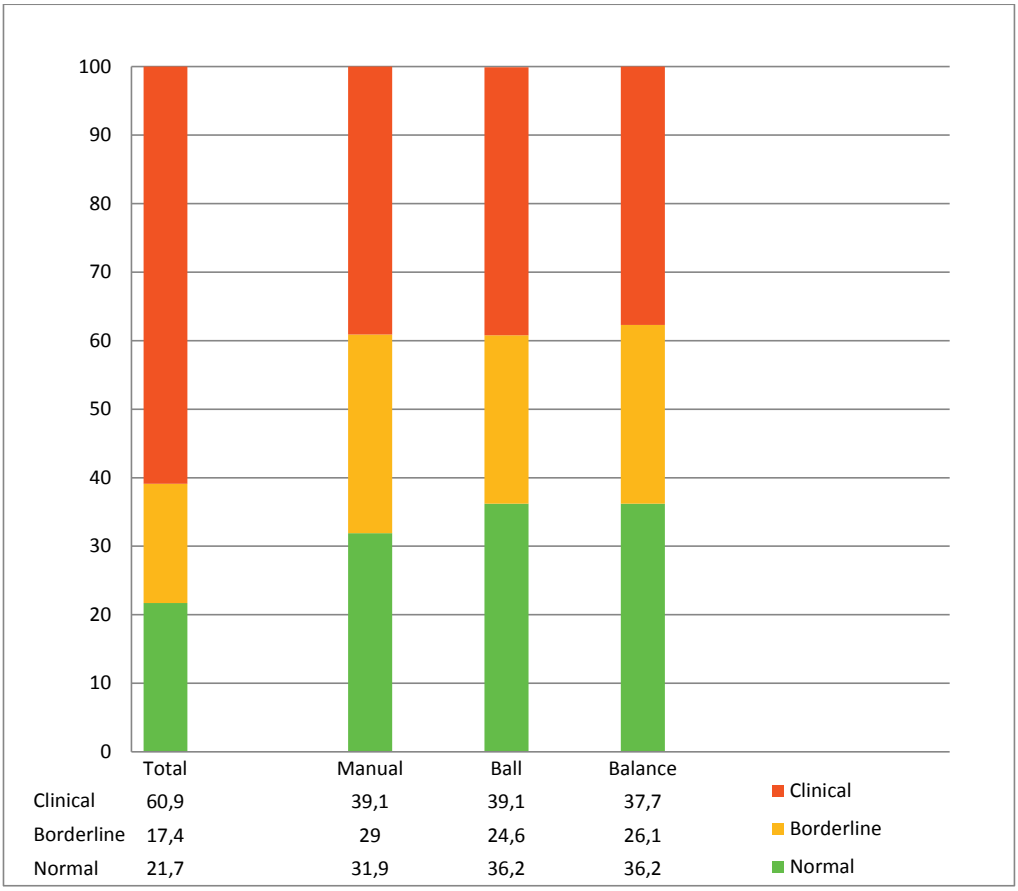
In multivariable ordinal regression analyses (Table 4; phase 2 with α set at .05), single variables within one block (type of education and hypermobility) had p values above α = .05 and so could not be used in multivariable models. In three blocks, final models yielded a limited amount of significant predictors. Since all seven children with an ASD classification scored within the

clinical range, the odds ratio of having borderline or clinical M-ABC scores could not be calculated and so ASD was left out of multivariable analyses. Also, the multivariable ordinal regression of ADHD and ASD could not be performed because all seven children with ASD classifications also had an ADHD classification. We compared the distribution of the M-ABC classification between the groups without ADHD or ASD versus the group with only ADHD versus the group with both ADHD and ASD using a Chi-squared test. This distribution did not differ significantly (χ^2 (4, N=69) = 7.53, p= .11), indicating that all three groups contributed independently to the distribution of motor problems.

The Externalising Problems scale was approaching significance as a predictor of motor outcome (p = .063). With low scores for Externalising Problems, the probability of a clinical score on the M-ABC was low. Children without externalising problems on the CBCL only had a 23% chance of a clinical score on the M-ABC, whilst children with externalising problems scores in the clinical range had an 81% chance, as is shown in Figure 3. Finally, intelligence (i.e. Performance IQ) was not found to be significantly associated with total motor problems.

Exploratory univariable linear regression analyses, with motor outcome on the M-ABC-2 as a continuous dependent variable (n = 34), found significant associations with independent variables: Internalising Problems scale (F (1,26) = 5.21; p =.031; R^2 = .17; β = -.13); Externalising Problems scale (F (1,26) = 6.99; p = .014; R^2 = .21; β = -.12); and Total Problems scale (F (1,26) = 6.15; p = .020; R^2 = .19; β = -.13), again indicating that an increase in emotional and behavioural problems is associated with a decrease in motor proficiency. Residuals for these regressions were normally distributed.

Figure 2. Classification of motor problems based on Movement ABC percentile scores (*n*= 69)



Clinical: Percentage of children with movement difficulty- scores below 6th percentile

Borderline: Percentage of children with scores from 6th to 15th percentile

Normal: Percentage of children with no movement difficulty- scores above 15th percentile

Table 3. Univariable ordinal logistic regression with separate variables predicting motor outcome (Movement ABC total scores; *n*=69)

			95% CI of Odds Ratio					
Variable	*Number*	*B (SE)*	lower	*OR*	upper	*Wald*	R^2	*p*
Age	69	0.08 (0.09)	0.77	0.93	1.12	4.31	.01	.429
Gender	69	0.56 (0.49)	0.22	0.57	1.49	1.31	.02	.253
Type of education	69	0.84 (0.58)	0.14	0.43	1.35	2.08	.04	.135$^{\#}$
Social economic status	69	-0.10 (0.19)	0.77	1.10	1.59	0.29	.01	.595
Mode of inheritance	69	-0.42 (0.49)	0.59	1.53	3.95	0.76	.01	.383
ADHD	69	1.01 (0.49)	0.14	0.36	0.96	4.22	.07	.038*
Using stimulant medication	69	-0.35 (0.54)	0.49	1.41	4.05	0.41	.01	.523
Autism spectrum disorder[a]	69	-	-	NA	-	-	.12	.035**
Hypotonia	69	0.28 (0.60)	0.23	0.76	2.47	0.21	<.01	.644
Hypermobility	69	0.98 (0.70)	0.10	0.38	1.49	1.94	.04	.140$^{\#}$
Scoliosis	69	0.25 (0.79)	0.28	1.28	5.97	0.10	<.01	.755
Writing problems at school	69	-0.20 (0.50)	0.46	1.22	3.25	0.16	<.01	.694
CBCL Internalising problems	58	- 0.04 (0.03)	0.99	1.04	1.09	2.23	.04	.134$^{\#}$
CBCL Externalising problems	58	- 0.04 (0.02)	0.10	1.04	1.09	3.30	.07	.063$^{\#}$
CBCL Total problems	58	-0.05 (0.03)	1.00	1.05	1.10	3.65	.08	.051$^{\#}$
Verbal IQ	68	0.01 (0.02)	0.96	0.99	1.02	0.41	.01	.519
Performance IQ	68	0.03 (0.02)	0.94	0.97	1.01	2.43	.04	.115$^{\#}$
Total IQ	69	0.03 (0.02)	0.94	0.97	1.01	2.10	.04	.141$^{\#}$

R^2 = Nagelkerke pseudo R^2 p-values of likelihood ratio chi-square; $^{\#}p$ <.20; $^{*}p$ <.05; $^{**}p$ <.01

[a] As there were no cases in cells with normal M-ABC-scores for children with an ASD classification, the estimate was minus infinity

Table 4. Multivariable backward ordinal logistic regression with variables from separate blocks predicting motor outcome (Movement ABC total classification; *n*=69)

			95% CI of OR					
Variables	*Number*	*B (SE)*	lower	*OR*	upper	*Wald*	R^2	*p*-value
Neuropsychiatric problems								
ADHD	69	1.01 (0.49)	0.14	0.36	0.96	4.22	.07	.038*
Autism spectrum disorder[a]	69	-	-	NA	-	-	.12	.035*
Emotional and behavioural problems								
Model 1	58						.07	.168
Internalising problems		-0.01 (0.03)	0.95	1.01	1.08	0.10		.757
Externalising problems		-0.04 (0.03)	0.98	1.04	1.10	1.44		.235
Model 2	58							
Externalising problems		-0.04 (0.02)	0.10	1.04	1.09	3.30	.07	.063
Intelligence								
Model 1	68						.04	.289
Performance IQ		0.03 (0.03)	0.91	0.97	1.04	0.71		.401
Total IQ		0.001 (0.03)	0.94	1.00	1.07	0.001		.973
Model 2	68							
Performance IQ		0.03 (0.02)	0.94	0.97	1.01	2.43	.04	.115

OR = Odds ratio; NA = Not Applicable R^2 = Nagelkerke pseudo R^2 *p*-values of likelihood ratio chi-square; $^{*}p < .05$; $^{**}p < .01$

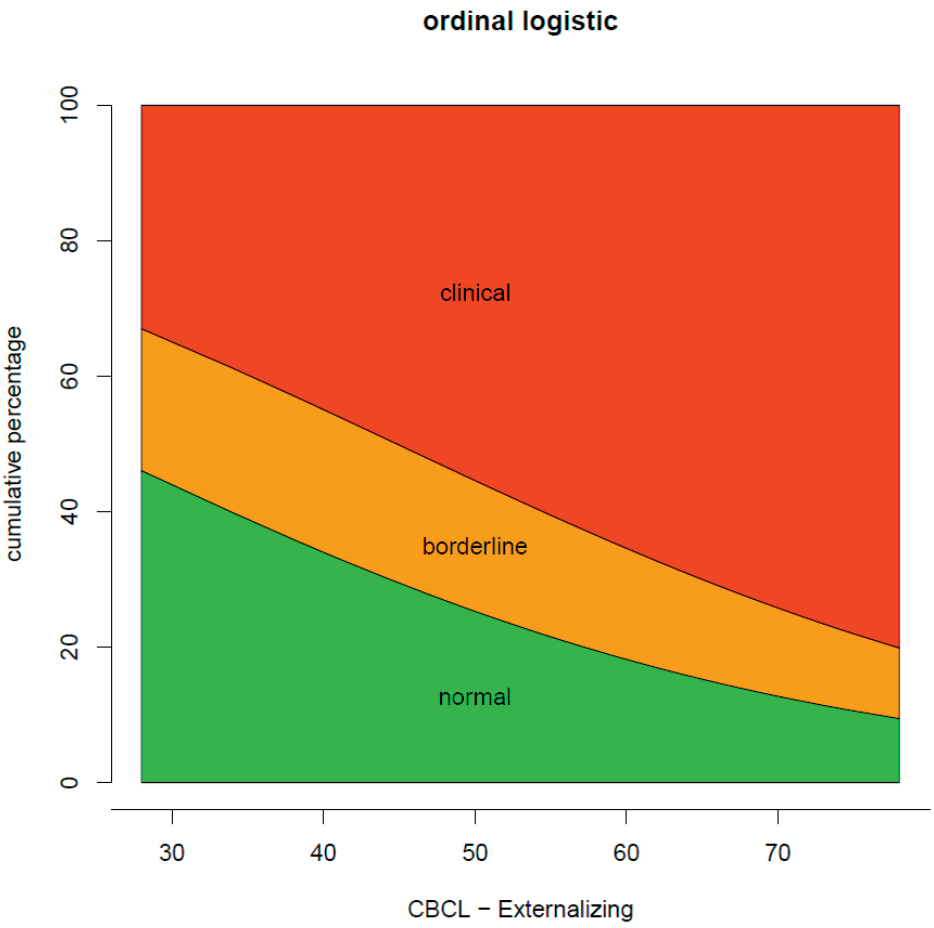
[a] As there were nog cases in cells with normal M-ABC-scores for children with an ASD classification, the estimate was minus infinity

Discussion

Our study shows that motor problems frequently occur in our group of children with NF1: 61% of these 69 children have serious motor problems and another 17% score within the borderline range. In the part of our cohort not evaluated in the expertise centre (*n*=90), 31 were already identified as having motor problems, resulting in an overall 46% (73/159) with serious motor

problems. The distribution of these groups and outcomes is visualized in Figure 1 in the Box with 'Total number clinical score'. Previous studies using broad motor test batteries found smaller or comparable proportions. One study in a comparable age range found 54% (14 out of 26 children) scoring between one and two standard deviations below average and another 27% (7/26) scored below 2 SD.[3] When comparing studies, one should realize that the cut-offs of the P5 and the P15 correspond to z-scores of 1.65 and 1.04 below average in the standard normal distribution.

Figure 3. Relationship between cumulative percentages of classification of total motor scores and scores on CBCL Externalising problems scale



Next to ADHD[26] and ASD symptoms[27], motor problems seem to be among the most common comorbid developmental problems of children with NF1. We found motor problems in a broad range of domains, comparable to the problems found in DCD.[8]

In our attempt to find predictors of motor outcome we did not find a significant contribution of demographic characteristics such as age, gender, or SES. A previous comparable study in a smaller sample did not find effects for age or gender either. [3] We also did not find associations with neurological and orthopaedic problems such as hypotonia, hypermobility, or scoliosis. Given the broad variability in these characteristics within our population (Table 1), we think our study population had sufficient power to detect potential associations if they existed. There was a limited association between (performance) intelligence and motor performance. Previous research [1] found that motor coordination and motor speed contributed to the performance on some subtests of the WISC. However, in our study we used a broader motor test battery such as the M-ABC and children were found to have serious motor problems in general, regardless of their overall intelligence. Since a previous study [9] found that poorer balance skills were associated with a reduced perceptual reasoning index, we performed an additional univariable ordinal logistic regression to specifically find out whether balance skills on the M-ABC were associated with performance IQ. Only a weak association was found with an odds ratio of 0.97 (95%CI, 0.93 to 1.00), Wald χ^2 (1) = 3.774, p = .052). Whether this finding is a reflection of an abnormal neurodevelopmental process underlying these abilities in children with NF1, may be a subject for future research.

Recent studies do provide evidence for a relation between motor experience and cognitive development in the first three years of life when at the same time this relation becomes less clear in older children. [28] The fact that we did not find a significant effect of age on motor performance, may presumably be caused by the fact we included children from 4 to 16 years old.

Externalising behavioural problems might be associated with motor outcome. This association was found to be significant in additional explorative analyses with standard scores of the children tested with the M-ABC-2. Also, ADHD was a significant predictor of motor outcome, and all children with an ASD classification had severe motor problems. Previous studies also found that motor problems often occur in children with emotional, behavioural, and pervasive developmental disorders.[29, 30] The co-occurrence of motor and behavioural problems could be an indicator of a more severe neurologic phenotype.[31] It is, however, unclear what the direction of

the association between behavioural and motor problems is. Longitudinal and treatment studies could elucidate this issue. Neuropsychiatric and motor problems have a large impact on participation in daily life, even more so when these problems occur simultaneously.

Limitations

Although NF1 is relatively rare, we succeeded in gathering data on the motor performance of 69 children over a 12-year period. However, our sample size is still small considering the number of variables incorporated into the regression analyses of this study. For this reason, there is a risk of overfitting, and care should be taken when drawing conclusions regarding the predictive value of variables. To avoid unnecessary assessments, we did not evaluate the motor performance of children who recently had such an assessment. In addition, since the assessment of motor performance was on a voluntary basis, children without any motor complaints were not required to visit our physiotherapist. For these reasons, we cannot exclude selection bias. We tried to correct for this bias by calculating the total amount of children scoring in the clinical range (Figure 1).

The cross-sectional design limits interpretations regarding the effect of age on motor performance. Probably, longitudinal research will be able to express this relationship in a more decisive way.

During the time period of this study, there was a move by physiotherapists in the Netherlands from using the first version of the Movement-ABC to the second version. For this reason, we were dependent on the categorical classification of motor problems as a primary outcome measure. This is a consequence of continuous sampling over a long period of time. One should be careful when combining data from both tests since the M-ABC-2 is an elaboration of the M-ABC-1, resulting in differences between both instruments. [32] Because the age range of the M-ABC was the starting point of this study, we used the two age-appropriate versions of the Wechsler scales and of the CBCL. Although the correlation between both versions is high, [19, 20] future research in larger groups could benefit from the selection of smaller age ranges.

For this study, we collected data from medical records. This resulted in missing information (as is shown in Table 2), particularly regarding emotional and behavioural problems, most likely because some parents failed to return questionnaires. Since all children were assessed using a standardized protocol, other data are relatively complete.

The proportion of children with ADHD symptoms is comparable to that in other studies,[26] but the percentage of children with ASD symptomatology in our study (10%) is somewhat lower than former prevalence estimates (21-40%).[33] In the group with ASD, all children appeared to have severe motor problems. Although this may suggest clinical relevance, we interpret this observation with care, due to the small sample size.

Clinical implications and recommendations

Developmental motor problems are frequently overlooked in clinical practice, yet they can have a considerable impact on children's lives.[34] Using a broad motor assessment in a large cohort of children with NF1, we showed a high prevalence of serious motor problems. These problems seem to be independent of age or intelligence. When children with NF1 show serious motor problems, the diagnosis of DCD might be considered as a comorbid problem. This is especially important in helping to recognise the impact of motor problems on daily life, and in allocating the correct treatment. Although the DSM-IV-TR[16] states that in DCD, 'the disorder is not due to a general medical condition', to our opinion NF1 does not have to be regarded as such. DCD could be used in practice as a descriptive diagnosis stressing the impact of motor problems on daily life.

Concerning participation in daily life, children with NF1 often experience problems with writing.[1, 35] It is important to find out whether people with NF1 experience further such difficulties in daily functioning such as in activities of daily living, play, sports, or with driving. This is of great importance since a decrease in participation could not only affect the practice of motor skills but also the development of social skills and quality of life in general.

Assessment and treatment of motor problems in NF1, especially in children with behavioural and social problems, should be considered at a young age, using a broad motor assessment battery. Early motor intervention can have a beneficial effect on behavioural problems, as is indicated by a study showing that in ADHD, [36] motor-affected children receiving physiotherapy presented less frequently with comorbid emotional and behavioural problems. The impact of physiotherapy and psychological therapy on motor functioning, motor participation, and emotional and behavioural problems in children with both NF1 and motor problems is unknown. However, considering the larger potential for plasticity at a young age, referral to both a physiotherapist and a psychologist could be considered at a young age in children with NF1.

Conclusion

More than half of the children with NF1 in this sample had severe motor problems. These problems seem to be independent of age or intelligence. Next to ADHD and ASD, motor problems are among the most frequent comorbid developmental problems in children with NF1. In this study, ADHD and ASD-symptomatology, and externalising behavioural problems are associated with motor problems. The combination of both motor and behavioural problems might result in a more severe phenotype of NF1. Because of their impact on participation in daily life, motor problems need to be specifically addressed in diagnosis, follow up and treatment of children with NF1.

Acknowledgements

We would like to thank all the children and families for participating in this study. A special thank you to Bethany Nicholson for her assistance and expertise, and Alma Weber and Annick Laridon for including many patients and for assistance during study conduct. We also thank clinicians throughout the Netherlands for referring patients.

References

1. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005;65:1037-1044.

2. Soucy EA, Gao F, Gutmann DH, Dunn CM. Developmental delays in children with neurofibromatosis type 1. J Child Neurol 2012;27:641-644.

3. Johnson BA, MacWilliams BA, Carey JC, Viskochil DH, D'Astous JL, Stevenson DA. Motor proficiency in children with neurofibromatosis type 1. Pediatr Phys Ther 2010;22:344-348.

4. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

5. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

6. Garg S, Lehtonen A, Huson SM, et al. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. Dev Med Child Neurol 2013;55:139-145.

7. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008;23:1002-1010.

8. Skinner RA, Piek JP. Psychosocial implications of poor motor coordination in children and adolescents. Hum Mov Sci 2001;20:73-94.

9. Champion JA, Rose KJ, Payne JM, Burns J, North KN. Relationship between cognitive dysfunction, gait, and motor impairment in children and adolescents with neurofibromatosis type 1. Dev Med Child Neurol 2014;56:468-474.

10. Hofman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: the cognitive phenotype. J Pediatr 1994;124:S1-8.

11. Lorenzo J, Barton B, Acosta MT, North K. Mental, motor, and language development of toddlers with neurofibromatosis type 1. J Pediatr 2011;158:660-665.

12. NIH nioh. Neurofibromatosis. NIH Consens Statement 1987 Jul 13-15. 1987;6:1-19.

13. Henderson SE, Sugden, D. A. Movement assessment battery for children manual. London: The Psychological Corporation Ltd., 1992.

14. Henderson S, Sugden, D., Barnett, A. Movement assessment battery for children-2 second edition [Movement ABC-2]. London: The Psychological Corporation, 2007.

15. Kort W, Schittekatte M, Dekker PH, et al. WISC-III NL; Wechsler intelligence scale for children, derde Editie NL. Handleiding en verantwoording Londen: Harcourt Assessment 2005.
16. Association AP. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000.
17. Planbureau SeC. Statusscores. In: "Rijksinstituut voor Volkgezondheid en Milieu: Ministrie van Volksgezondheid WeS, ed. Nederland2012.
18. G. van der Steene AB. Wechsler Preschool and Primary Scale of Intelligence- Revised, Dutch version (WPPSI-R), manual. Lisse, the Netherlands: Swets and Zeitlinger BV, 1997.
19. Weschler D, Hendriksen J, Hurks P. WPPSI-III-NL, Wechsler preschool and primary scale of intelligence. Nederlandse bewerking. London: Pearson Assessment and Information BV, 2009.
20. Achenbach T, Rescorla, LA. Multicultural Supplement to the Manual for the ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families, 2010.
21. Verhulst F, Van der Ende, J. Handleiding ASEBA: Vragenlijsten voor Leeftijden 6 t/m 18 jaar. Rotterdam: ASEBA Nederland, 2013.
22. IBM SPSS Statistics for Windows, Version 20.0 [computer program]. Armonk, NY: IBM Corp., 2011.
23. Team RDC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2008.
24. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Academic Press, New York, 1988.
25. Steyerberg E. Clinical Prediction Models: A Practical Approach to Development, Validation,and Updating. New York: Springer, 2009.
26. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Dev Med Child Neurol 2002;44:164-170.
27. Garg S, Plasschaert E, Descheemaeker MJ, et al. Autism spectrum disorder profile in neurofibromatosis type I. J Autism Dev Disord 2015;45:1649-1657.
28. Libertus K, Hauf P. Editorial: Motor Skills and Their Foundational Role for Perceptual, Social, and Cognitive Development. Front Psychol 2017;8:301.
29. Emck C, Bosscher R, Beek P, Doreleijers T. Gross motor performance and self-perceived motor competence in children with emotional, behavioural, and pervasive developmental disorders: a review. Dev Med Child Neurol 2009;51:501-517.

30. Fliers E, Rommelse N, Vermeulen SH, et al. Motor coordination problems in children and adolescents with ADHD rated by parents and teachers: effects of age and gender. J Neural Transm (Vienna) 2008;115:211-220.

31. Peters LH, Maathuis CG, Hadders-Algra M. Children with behavioral problems and motor problems have a worse neurological condition than children with behavioral problems only. Early Hum Dev 2014;90:803-807.

32. Brown T, Lalor A. The Movement Assessment Battery for Children--Second Edition (MABC-2): a review and critique. Phys Occup Ther Pediatr 2009;29:86-103.

33. Garg S, Plasschaert E, Descheemaeker MJ, et al. Autism Spectrum Disorder Profile in Neurofibromatosis Type I. J Autism Dev Disord 2014.

34. Baird G, Santosh PJ. Interface between neurology and psychiatry in childhood. J Neurol Neurosurg Psychiatry 2003;74 Suppl 1:i17-22.

35. Gilboa Y, Josman N, Fattal-Valevski A, Toledano-Alhadef H, Rosenblum S. The handwriting performance of children with NF1. Res Dev Disabil 2010;31:929-935.

36. Fliers EA, Franke B, Lambregts-Rommelse NN, et al. Undertreatment of Motor Problems in Children with ADHD. Child Adolesc Ment Health 2009;15:85-90.

CHAPTER 3.

Development of emotional and behavioral problems in neurofibromatosis type 1 during young childhood

Rietman AB, Oostenbrink R, van Noort K, Franken MJP, Catsman-Berrevoets CE, Aarsen FK, Hendriksen JG, de Nijs PFA

American Journal of Medical Genetics part A 2017;173:2373-2380

Abstract

This retrospective longitudinal study in young children with neurofibromatosis type 1 (NF1) aimed to identify if, and how early problems in behavior, intelligence, and language development are associated with later behavioral problems. At the first assessment at preschool age, we evaluated language skills, intelligence, and emotional and behavioral problems as reported by parents. The second assessment at school-age we evaluated intelligence, and emotional and behavioral problems as reported by parents and teachers. Association of baseline assessments with secondary assessment was evaluated using multivariable linear regression analysis.

Of the 61 patients (25 males, 36 females; mean age 4;5 years [*SD* 1;1 years]) with NF1 who had a first assessment, 38 children (21 males, 17 females; mean age 7;11 years [*SD* 2;1 years]) had a second assessment after a mean period of 3;5 years. Longitudinal data on behavioral problems were collected for 23 of these children. Intelligence and language development were not associated with internalizing problems. Parent-rated internalizing behavioral problems significantly increased with age in this subgroup. Baseline internalizing problems predicted later internalizing problems (adjusted R^2=0.33, *p*=.003). The presence of these problems at pre-school age may be predictive of internalizing problems at a later age.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disease with an estimated birth incidence of 1 in 2,700 [1]. As a neurocutaneous disorder, NF1 presents with readily visible features such as café-au-lait spots and neurofibromas, but cognitive and behavioral problems are also central to the disorder [2]. Cognitive deficits include below-average IQ (intelligence quotient) scores[3] and impairments in attention, executive functioning, visuospatial skills, motor skills, and language [2]. Behavioral problems in children with NF1 consist mainly of emotional and social problems [4, 5]. Parents mainly report internalizing problems, which encompasses social withdrawal, somatic complaints, anxiety, and depression [6, 7]. Speech and language problems, such as delays in speech and language development, articulation disorders, and expressive and receptive language development disorders, affect toddlers and school-aged children, as well as adults with NF1 [8-13].

Longitudinal studies in neurogenetic disorders are relatively scarce [14]. A study in 19 children [15] , initially between 6 and 13 years old, concluded that children with NF1 scored lower on cognitive tests than their unaffected siblings, but over time, their patterns of growth were not different from those of their siblings. In a follow-up study in 11 children with NF1 from 12 to 20 years old, Hyman et al. [16] observed no overall change in general cognitive ability. A longitudinal study in 43 children under eight years of age [17] found an increase with age of the number of areas of delay. Recently, longitudinal studies following patients with NF1 over a period of several years, focused on MRI data and general cognition as outcome measures [18, 19]. The first study followed 67 children aged 6 to 17 years over a three-year period; the second study retested 18 patients aged 8 to 33 years over an 18-year period. Both studies observed improvement of IQ with age in the group of patients with discrete MRI T2 hyperintensities. A recent study by Lorenzo et al [20] followed 39 toddlers from 21 to 40 months of age and found no change in parent rated behavioral scores between children of 21, 30 and 40 months old.

In the general population, the proportion of parent- and teacher-rated emotional and behavioral problems is stable at preschool age and a predominantly internalizing profile only emerges at 6 years [21]. Children with parent- or teacher rated internalizing problems at school entry (aged 4-5 years) have a greater chance of internalizing problems at preadolescence (aged 10-11 years). The same applies for externalizing problem behavior [22].

The aim of this longitudinal study in children between 4;5 and 7;11 years old was to identify whether problems in behavior, intelligence, and language development are associated with later behavioral problems, to inform future planning of interventions.

Materials and methods

Patients and moments of assessment

In the Erasmus MC, Sophia Children's Hospital in Rotterdam, the Netherlands, patients with NF1 visit the outpatient clinic yearly. All patients with NF1 between the ages of 2 years 3 months and 6 years 3 months are routinely referred for a first neuropsychological assessment and speech and language evaluation (at time point 1; T1). At primary school (T2), the same patients were offered a second neuropsychological evaluation in the outpatient clinic of the Erasmus MC or in the Kempenhaeghe Centre for Neurological Learning Disabilities (KCNL). The children who participated in the second evaluation were evaluated by a pediatric neurologist and a neuropsychologist. For this study, we included all patients who were evaluated between 2002 and 2010 and met the National Institutes of Health diagnostic criteria for NF1 [23]. Clinical and demographic data for this study were obtained from patient records, as registered by the pediatrician of the NF1 team. Familial or sporadic NF1 was determined from family history. According to a standard evaluation of hearing abilities by an audiologist, no child had a hearing loss greater than a slight, temporary impairment [24].

This study was approved by the Medical Ethical Committee of Erasmus MC, Sophia Children's Hospital.

Outcome measures

Emotional and behavioral problems were the main outcome at both time points. Additionally, we report outcomes on intelligence and language development at the first assessment (T1) and on intelligence at the second assessment (T2). Because of the importance of detecting early problems in language development, cognition was evaluated by testing language development and non-verbal intelligence separately at T1. Receptive language was tested with the Dutch version of the Reynell Developmental Language Scales (RDLS) [25]. Expressive language was evaluated using the Dutch version of the Schlichting Expressive Language Test (SELT)[26]. Both tests are designed for

children aged 14 months to 6 years 3 months. The word development part of the SELT measures expressive vocabulary skills by asking the child to name objects or pictures. The sentence development part evaluates the level of grammatical skills (syntactic and morphological) by using functional imitation as an elicitation technique. Both RDLS and SELT provide norm-referenced scores, based on typical language levels for normally developing children. The RDLS yields a language comprehension quotient (LCQ). Scores on the SELT word development scale and on the sentence development scale are expressed in a word development quotient (WDQ) and a sentence development quotient (SDQ).

Intelligence at T1 was assessed with the Snijders-Oomen Non-verbal revised intelligence scale for young children (SON-R 2½-7; [27]) a non-verbal intelligence scale suitable for all children from age 2 years 3 months to 7 years 3 months. It is particularly suited for children with hearing impairments and/or language or verbal communication deficits and consists of six subtests resulting in a Total IQ, a Performance Scale IQ, and a Reasoning Scale IQ.

At T2, intelligence was measured with the Wechsler Preschool and Primary Scale of Intelligence- Revised, Dutch version (WPPSI-R)[28] or the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL; [29]. The WPPSI-R and the WISC-III-NL are intelligence tests for children, the first for children aged 2 years 6 months to 7 years 7 months, the second for children aged 6 to 17 years. The tests consist of several subtests resulting in a Full-scale IQ, Verbal IQ, and Performance IQ. All intelligence and language tests have a population mean of 100 and an *SD* of 15.

At both T1 and T2, parents completed age-appropriate version of the Child Behavior Checklist (CBCL) to assess emotional and behavioral problems, either with the preschool version, the CBCL/1 ½-5 [30], or with the school-aged version, CBCL/6-18 [31]. These both forms differ in items and scales but both report summary scales for internalizing, externalizing and total problems. At T2, teachers were asked to complete the Teacher's Report Form [31]. Scores were converted to T scores (Mean 50, *SD* 10), where a higher score corresponds to more problems. Summed scores result in three broad-band scales for Internalizing, Externalizing, and Total Problems. On these scales for Internalizing, Externalizing, and Total Problems, T scores from 60 to 62 are considered to fall in a borderline clinical range, whilst T scores of 63 and higher are considered to fall within the clinical range.

Analysis

All data were analyzed using SPSS, version 20 [32]. Two-sided independent t-tests were used for comparisons of group means within one time point for continuous, normally distributed variables. Two-sided paired samples t-tests were used for comparisons between two time points (T1 versus T2). Wilcoxon signed ranks test for two related samples was used for non-normally distributed data and for small samples. Effect sizes were calculated for all t-tests using Cohen's d. Effect sizes were considered small from 0.2 to 0.5, moderate from 0.5 to 0.8, and large if >0.8 [33]. The Shapiro-Wilk test was used to control for normal distribution.

Correlation analyses with the use of the Pearson correlation coefficient or Spearman's ρ for non-normally distributed data were performed to describe the association between outcome measures.

Multivariable linear regression models were constructed to analyze independent factors predicting outcomes with the largest difference between T1 and T2. In preparing analyses, we used the 'rule-of-thumb': one variable for every 10 participants [34]. The cut-off level for significance was set at α=.05.

Results

Patients

Sixty-one patients visited the outpatient clinic between 2002 and 2010 at time point 1 (T1) for evaluations by the speech/language therapist and the neuropsychologist (Table 1). The mean age of the children at T1 was 4;5 years (*SD*=1;1, range 2;3 to 6;3 years). At time point 2 (T2) 38 children (62%; mean age 7;11 years (range 5;0–13; 6 years; *SD*=2;1 years) had a second neuropsychological evaluation, including an intelligence test. Between T1 and T2 the mean interval was 3;5 years (range 1;1–7;10 years; *SD*=1;10 years). A flow chart of included patients is presented in Figure 1.

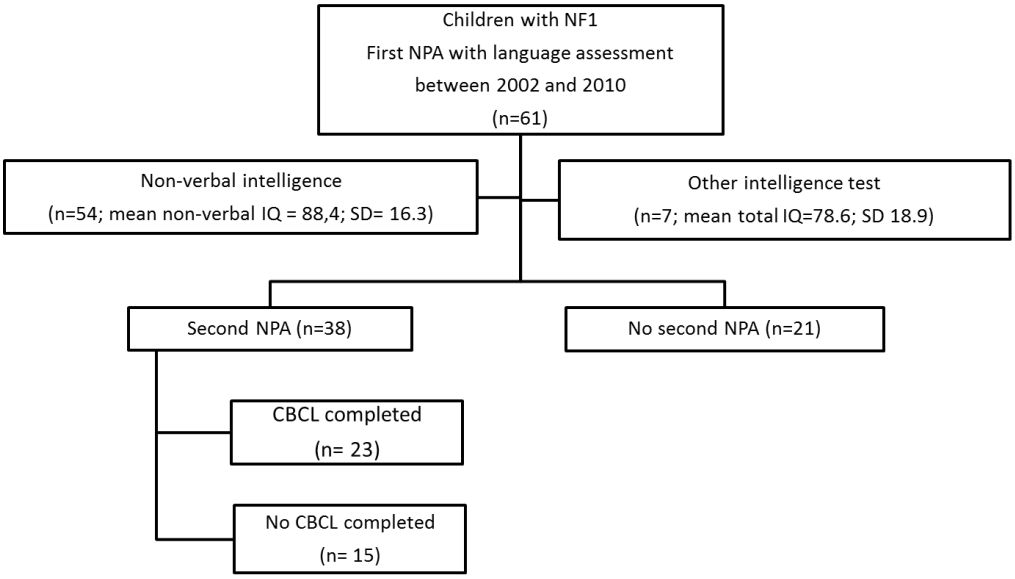
Table 1. Characteristics of children with NF1 at baseline (T1) and follow-up assessment (T2)

	No.	%	No.	%
Demographic characteristics	Time point 1 (*n*=61)		Time point 2 (*n*=38)	
Mean age in years (*SD*)	4;5 (1;1)		7;11 (2;1)	
Male gender	25	41	21	58
Familial NF1[a]	27	44	21	58
Special education[ab]	3	5	11	29
Speech-language therapy at T1	14	23	10	26

[a] Leaving out 1 child with incomplete file

[b] Attending a special school for children with learning and/or behavioral problems

Figure 1. Flowchart of patient inclusion



Abbreviations:

NF1 : Neurofibromatosis type 1

NPA : Neuropsychological assessment

CBCL : Child Behavior Checklist

Language development, intelligence, and behavioral problems at T1 (Table 2 and 3)

Scores on measures for language, intelligence, and behavior did not differ between boys and girls. Comparing the group with familial NF1 to the non-familial group, scores differed significantly on the three subtests for language development: RDLS LCQ (t_{58}=2.381, p=.021), SELT WDQ (t_{51}= 2.030, p=.048), and SELT SDQ (t_{51}=2.039, p=.047), with lower scores for the familial NF1-group with moderate effect sizes (0.62, 0.56 and 0.56). There was no significant difference between these two groups for intelligence and behavioral scores. The receptive language development (RDLS LCQ) of three children (5%) was below 70, possibly indicating severe problems in this area. Expressive language development was below 70 for three children on the SELT test for word development. No children scored below 70 on the test for sentence development. However, seven children (11%) could not complete the language assessment because of limited attention span or an inability to imitate. Fourteen children (23%) had speech and language therapy before assessment. After this assessment, all these children were advised to continue therapy and another 20 children (33%) were advised to start therapy.

Seven children (11%, different from the seven above) were evaluated for intelligence with intelligence tests or developmental screenings other than the SON-R. The average IQ of these children (M= 83.7; SD=17.1) did not differ significantly from the IQ of the other 54 children (M= 88.4; SD=16.3).

According to the scores on the CBCL parent rating scale, 25% of the children (11/44) scored within the borderline or clinical range with their Total Problems score. Fifteen percent (7/48) of them also scored within this range for the Internalizing Problems score and 23% (11/48) for the Externalizing problems score. There was no significant difference between Internalizing and Externalizing Problems scores at T1 (p=.158).

Table 2. Scores on intelligence and language tests at baseline (T1) and follow-up (T2) assessment

	T1; *n*=61 Mean age 4;5 (*SD* = 1;1)			T2; *n*=38 Mean age 7;11 (*SD* = 2;1)		
	n	**Mean**	***SD***	***n***	**Mean**	***SD***
SON[a] Total IQ[b]	54	88.4	16.3			
SON Reasoning IQ	55	93.5	16.0			
SON Performance IQ	54	86.8	16.1			
RDLS LCQ[c]	61	92.9	14.5			
SELT WDQ[d]	54	92.5	15.3			
SELT SDQ[e]	54	92.7	11.4			
Full scale IQ[f]				38	85.3	15.0
Verbal IQ[f]				36	88.1	16.8
Performance IQ[f]				36	85.2	15.9

[a] SON: Snijders-Oomen Non-verbal intelligence test

[b] All cognitive and language tests compared to normative population (*M* = 100; *SD* = 15)

[c] Reynell Developmental Language Scales- language comprehension quotient

[d] Schlichting Expressive Language Test- word development quotient

[e] Schlichting Expressive Language Test- sentence development quotient

[f] Wechsler Preschool and Primary Scale of intelligence, Revised Dutch version or Wechsler Intelligence Scale for Children, third version for the Netherlands

Table 3. Scores on emotional and behavioral problems at baseline and follow-up assessment

	T1; *n*=61 Mean age 4;5 (*SD*=1;1)				T2; *n*=38 Mean age 7;11 (*SD*=2;1)			
	n	**Mean**	***SD***	***n* (%) scoring in borderline or clinical range[a]**	***n***	**Mean**	***SD***	***n* (%) scoring in borderline or clinical range[a]**
CBCL[b] Total Problems	44[c]	51.5	11.8	11 (25)	23[e]	60.8	12.7	12 (50)
CBCL Internalizing	48[d]	49.8	11.3	7 (15)	23[e]	60.7	11.2	14 (58)
CBCL Externalizing	48[d]	51.2	11.5	11 (23)	23[e]	55.2	12.8	10 (42)
TRF[f] Total Problems					21	57.7	8.7	10 (48)
TRF Internalizing					21	56.9	9.4	9 (43)
TRF Externalizing					21	53.0	9.3	6 (29)

[a] Behavioral Problems scores within the borderline clinical range (T score >59)

[b] Child Behavior Checklist; all behavioral questionnaires compared to normative population (*M* = 50; *SD* = 10).

[c] Total problem scores of 4 participants were not reported in patient records.

[d] Of these 48, 3 parents completed the CBCL/ 1 ½ -5 and 45 completed the CBCL/ 6-18

[e] Of these 23, 2 parents completed the CBCL/ 1 ½ -5 and 21 completed the CBCL/ 6-18

[f] Teacher Report Form

Intelligence and behavioral problems at T2

Twenty-three parents (61%) and 21 teachers (55%) completed and returned the CBCL/TRF questionnaires. These 23 children had a mean age of 4;5 years at T1 and of 8;5 years at T2. Within this group, half of the children had familial NF1 (50% for CBCL and 52% for TRF). There were no significant differences between the scores for boys or girls, or between the groups with familial or non-familial NF1. The 23 patients in the final group with a CBCL at T1 and T2 did not differ from the 15 patients without a CBCL at T2 in any of the demographic scores nor in IQ-scores. Correlations between parent and teacher ratings were significant for Internalizing (r=0.69, p=.001) and for Total Problems scores (r=0.53, p=.019), but not for Externalizing Problems scores.

Comparison between T1 and T2

The group which participated in the assessments at T1 but not at T2 (n=23) was compared to the group which participated at both time points (n=38). Both groups neither differed in any of the scores nor in demographic variables, except for mode of transmission (familial or sporadic NF1). The group which had an assessment at T2 consisted of more children with familial NF1 (55%) compared to the group which was not assessed at T2 (27%) (χ^2_1=4.4, p=.04).

Although the intelligence tests at T1 and T2 differed, no significant difference was observed between Total IQ scores on both tests in children who had assessments at both T1 and T2. Scores on the SON-R as a non-verbal test at T1 also did not differ from Performance IQ at T2. The most striking difference is an increase in Internalizing Problems scores at T2 (M=61.3, SD=11.1) compared to T1 (M=52.6, SD=11.4) (Z=237.5, p<.001) in the scores of these 23 children, with a moderate effect size (0.77). With post-hoc power calculations based on this effect size and a sample size of 23, we found the power (*1- beta*) to be .93. Over a mean period of 3.4 years, the Internalizing Problems score increased with more than one standard deviation (10.9 points). Consequently, Total Problems scores differed significantly between T1 and T2 (p=.02, moderate effect size 0.77). Externalizing Problems scores did not change significantly as indicated by a small effect size (0.09). In a single linear regression model, baseline internalizing problems predicted later internalizing problems (adjusted R^2 = 0.33, p = .003). Individual changes in CBCL Internalizing T-scores are presented in Figure 2.

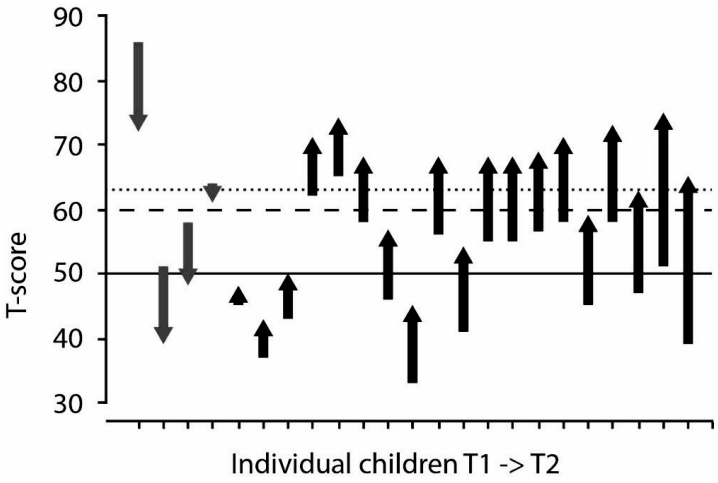


Figure 2. Individual differences in T scores on the CBCL Internalising Problems scale between baseline (T1) and follow-up (T2) (*n*=23). Decreases (light grey arrows) and increases (dark grey arrows) arranged in order of magnitude of change. The solid line represents population mean (T score=50), dashed line indicates lower limit of borderline scores (T score=60), dotted line indicates lower limit of clinical scores (T score=63).

Multivariable linear regression

Because particularly the Internalizing Problems score increased from T1 to T2, this variable was selected as the main dependent variable in regression analyses. To explore the predictive quality of each predictor separately, each of the variables at T1 from Tables 1 and 2 and length of follow-up time were entered into a linear regression model (backward method), with Internalizing Problems scores at T2 as dependent variable, controlling for Internalizing Problems scores at T1. None of the variables at T1 contributed significantly to the regression equation. Also IQ at T2 was not found to be of predictive value. This corresponds with the low, non-significant correlations between Internalizing Problems scores and intelligence at T1 (*N*=34) and T2 (*N*=23).

Discussion

The present study investigates the development over time of parent-reported behavioral problems in young children with NF1 and the influence of intelligence, language development, and early behavioral problems. In accordance with other studies [35], we did not find an elevated level of behavioral problems in young children (mean age 4;5 years), but we did find more internalizing

problems at a later age (mean age 7;11 years), compared to a normative sample. Higher rates of internalizing problems indicate more anxious, withdrawn and depressed behavior and/or more somatic complaints. Other, non-longitudinal studies also found more internalizing than externalizing problems in children with NF1 [7, 8, 36]. Our most prominent finding is a significant increase of parent-reported internalizing problems with age, as opposed to Lorenzo et al.[20], who found no differences over time in younger children (1y 9mo to 3y 4mo). Considering their findings, this would imply that changes in internalizing behavior in these children with NF1 occurred at kindergarten-age but possibly not before.

In our study, gender, age, non-verbal intelligence, and language development at T1 did not contribute significantly to behavioral problems at T2. In addition, intelligence scores at T2 did not correlate significantly with internalizing or externalizing problems at T2. This is in line with previous research [37] in which internalizing and externalizing behavioral problems did not correlate significantly with IQ-measures. In our study, only pre-existing internalizing problems at T1 predicted internalizing problems at a later age in children with NF1. Verhulst and Van der Ende [38] suggested that internalizing problems appearing in preschool children tend to persist over time. In our study, the internalizing problems not only persisted, but in 19 out of 23 children, these problems increased. The scores of most of these children moved into the clinical range, as shown in Figure 2. This increase is hard to explain when only relying on the current dataset. Only expressive grammatical language development had a possibly meaningful but nonsignificant contribution to the effect of initial internalizing problems (adjusted R^2 increased from .35 to .44 with CBCL at T1: standardized beta= .52; p= .01 and SELT SDQ at T1: standardized beta= -.31; p= .10). Possibly, a delay in expressive language development affects social and emotional development, worsening internalizing behavioral problems [39, 40]. In addition, internalizing problems in young children may remain unnoticed and thus untreated [41] leading to an increase of these problems.

Intelligence and the rate of familial versus non-familial patients in this group are comparable to those in former samples of children with NF1. Non-verbal IQ at T1 and Full Scale IQ at T2 were in accordance with the Full Scale IQ of 86 in children with NF1, found by Krab et al.[3]. In our study, 33 of the children at T1 (55%) had a de novo mutation, which falls between the estimates of de novo mutation rates by Evans et al. ([1]; 42%) and Van Minkelen et al. ([42]; 74%). Having familial NF1 appeared to be a significant factor in language development, since these children scored lower on all language scales. Having a parent with NF1 might influence language

development. Whether this could be explained by genetic or sociocultural transmission is unclear and possibly a subject for further study.

Strengths and limitations

In neurogenetic disorders such as NF1, systematic follow-up is not obvious and sample sizes of longitudinal studies are generally small. This retrospective, longitudinal study follows the development of a sample of children with NF1. Because of the voluntary nature of the assessments offered, only 38 out of 61 children were assessed at two time points and out of these 38, 23 CBCL's were available. This loss to follow-up may affect the representativeness of this sample and so the generalizability of the results and the conclusions of this study. The decrease in sample size could result in attrition bias: maybe particularly parents with children who have more severe (behavioral) problems return for a second evaluation. Since the intelligence scores at T1 and T2 are comparable and similar to the scores previously found in children with NF1 in our center [3], we assume that results are not biased by a selection in cognition. The dropout on T2 because of unavailability of CBCL's is another point of concern. We tried to estimate its effect by comparing the groups with and without CBCL on all available variables and did not find any differences. One could argue that mainly parents of children with severe or increasing (internalizing) problems returned for an evaluation at T2. Next to this, there is a wide variability in the length of follow-up time. This however did not contribute to the observed differences in internalizing problems scores.

The difference in questions and scales of the CBCL/1 ½-5 and the CBCL/6-18 could be regarded as another limitation. In the first, subscales of the Internalizing Problems scale are Emotionally Reactive, Anxious/Depressed, Somatization, and Withdrawn. In the second, these are Anxious/Depressed, Withdrawn, and Somatic problems. Most preschool scales have a clear counterpart in the school-age scales. The correlation between the Internalizing Problems scales of the preschool and the school-age forms is between .39 and .61 [43]. Unfortunately, we did not have the scores on all the subscales, so we could not point out which of the subscales made the difference. Since former research did not show a difference between the scores on the separate subscales for Internalizing Problems [8, 36], we expect that the difference could be an effect of an increase in scores on all these subscales.

Measuring internalizing problem behavior in young children in an objective way is difficult and the validity of parental report could be disputed. However, there is no gold standard in

assessing behavioral problems in children, and both CBCL and TRF discriminate well between referred and non-referred populations [44]. Although it seems hard to measure this construct, test-retest reliability of the CBCL for young children is .81 and the internal consistency of the Internalizing scale is .94 [45]. Because the data in this study were retrieved from patient records, only the scores on main scales of CBCL and TRF were available, but not on items or syndrome scales. Future research could focus on the nature of internalizing problems in young children and on variables that are predictive of later behavioral problems such as family functioning, ADHD and ASD (Autism Spectrum Disorder) behavior, and social economic status. Particularly the development of ASD symptoms is of interest. A recent cross-sectional study found an increase of social difficulties when comparing children with NF1 before and after the age of 8 years [46]. Internalizing problems as found in our study include withdrawn behavior. These behaviors could be related to social problems such as autism at a later age.

Clinical implications

In the general population, early preschool internalizing problems are predictive of DSM-IV diagnoses at school age [47]. More specifically, internalizing behavior such as anxious and depressed behavior is predictive of later mood disorders [48]. The risk of mood disorders increases in early adolescence. In the light of our findings, caregivers should be sensitive to psychopathology in children and adolescents with NF1, especially to those that showed early problems in this area. In early and regular evaluations of emotional and behavioral problems in children with NF1, internalizing problems such as anxiety and depression should be a major point of concern. Both externalizing and internalizing problems can cause severe stress in families and schools. Early behavioral and psychosocial interventions should aim to support children and their parents and to reduce emotional and behavioral problems in children with NF1. Fortunately, internalizing problem behaviors are generally responsive to treatment [49].

Next to this, especially children with familial NF1 should have an assessment of language and cognition at preschool. To confirm our observations from this incomplete follow-up, we are currently evaluating the development of children with neurocognitive genetic disorders over a broad age-range, at fixed ages, with a fixed battery of neuropsychological tests, facilitating comparability between constructs and ages.

Conclusions

This study suggests a risk of increasing parent-reported internalizing behavioral problems in children with neurofibromatosis type 1. These problems seem to increase between the ages of four and eight years. Early internalizing problems at preschool may be determinants of internalizing problems at a later age. This underlines the importance of behavioral assessment at a young age. Future prospective research will help to identify risk factors to guide the focus of intervention programs.

Acknowledgments

We would like to thank all the children and families for participating in this trial. A special thank you to members of the ENCORE Expertise Centre for Neurodevelopmental Disorders, particularly Ype Elgersma, Arja de Goede-Bolder, Henriëtte Moll, Thijs van der Vaart, and Marie-Claire de Wit, and to Sandra Ansems-Klootwijk, Alma Weber and Bethany Nicholson for assistance during study conduct and for valuable discussions. We also thank clinicians throughout the Netherlands for referring patients, and the Dutch patient's organization (Neurofibromatose Vereniging Nederland) for their ongoing support.

References

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

2. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

3. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008;23:1002-1010.

4. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-563.

5. Huijbregts SC, de Sonneville LM. Does cognitive impairment explain behavioral and social problems of children with neurofibromatosis type 1? Behav Genet 2011;41:430-436.

6. Noll RB, Reiter-Purtill J, Moore BD, et al. Social, emotional, and behavioral functioning of children with NF1. Am J Med Genet A 2007;143A:2261-2273.

7. Graf A, Landolt MA, Mori AC, Boltshauser E. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. J Pediatr 2006;149:348-353.

8. Dilts CV, Carey JC, Kircher JC, et al. Children and adolescents with neurofibromatosis 1: a behavioral phenotype. J Dev Behav Pediatr 1996;17:229-239.

9. M. Lorch RF, J. Golding, R. Whurr. The nature of speech and language impairment in adults with neurofibromatosis 1. Journal of neurolinguistics 1999;12:157-165.

10. Hyman SL, Arthur Shores E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Dev Med Child Neurol 2006;48:973-977.

11. Thompson HL, Viskochil DH, Stevenson DA, Chapman KL. Speech-language characteristics of children with neurofibromatosis type 1. Am J Med Genet A 2010;152A:284-290.

12. Lorenzo J, Barton B, Acosta MT, North K. Mental, motor, and language development of toddlers with neurofibromatosis type 1. J Pediatr 2011;158:660-665.

13. Brei NG, Klein-Tasman BP, Schwarz GN, Casnar CL. Language in young children with neurofibromatosis-1: relations to functional communication, attention, and social functioning. Res Dev Disabil 2014;35:2495-2504.

14. Fisch GS, Carpenter N, Howard-Peebles PN, Holden JJ, Tarleton J, Simensen R. The course of cognitive-behavioral development in children with the FMR1 mutation, Williams-Beuren syndrome, and neurofibromatosis type 1: The effect of gender. Am J Med Genet A 2010;152A:1498-1509.

15. Cutting LE, Huang GH, Zeger S, Koth CW, Thompson RE, Denckl MB. Growth curve analyses of neuropsychological profiles in children with neurofibromatosis type 1: specific cognitive tests remain "spared" and "impaired" over time. J Int Neuropsychol Soc 2002;8:838-846.

16. Hyman SL, Gill DS, Shores EA, et al. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. Neurology 2003;60:1139-1145.

17. Wessel LE, Gao F, Gutmann DH, Dunn CM. Longitudinal analysis of developmental delays in children with neurofibromatosis type 1. J Child Neurol 2013;28:1689-1693.

18. Feldmann R, Schuierer G, Wessel A, Neveling N, Weglage J. Development of MRI T2 hyperintensities and cognitive functioning in patients with neurofibromatosis type 1. Acta Paediatr 2010;99:1657-1660.

19. Payne JM, Pickering T, Porter M, et al. Longitudinal assessment of cognition and T2-hyperintensities in NF1: an 18-year study. Am J Med Genet A 2014;164A:661-665.

20. Lorenzo J, Barton B, Arnold SS, North KN. Developmental trajectories of young children with neurofibromatosis type 1: a longitudinal study from 21 to 40 months of age. J Pediatr 2015;166:1006-1012 e1001.

21. Basten M, Tiemeier H, Althoff RR, et al. The Stability of Problem Behavior Across the Preschool Years: An Empirical Approach in the General Population. J Abnorm Child Psychol 2016;44:393-404.

22. Mesman J, Bongers IL, Koot HM. Preschool developmental pathways to preadolescent internalizing and externalizing problems. J Child Psychol Psychiatry 2001;42:679-689.

23. Neurofibromatosis. Natl Inst Health Consens Dev Conf Consens Statement 1987;6:1-7.

24. WHO WHO. Prevention of deafness and hearing impaired grades of hearing impairment [online]. Available at: http://www.who.int/pbd/deafness/hearing_impairment_grades/en/index.html. .

25. Eldik MCMv, Schlichting, J. E. P. T., Lutje Spelberg, H.C., Meulen, B.F. van der, Meulen, Sj. van der. Reynell Test voor Taalbegrip (Reynell test for language comprehension), manual. Nijmegen: Berkhout Nijmegen B.V., 1995.

26. Schlichting JEPT, Eldik, M.C.M. van , lutje Spelberg, H.C., Meulen, Sj. van der, Meulen, B.F. van der. Schlichting Test Voor Taalproductie (Schlichting test for language comprehension). Amsterdam, The Netherlands: Pearson Assessment and Information B.V, 1995.

27. Tellegen PJ, Winkel, M., Wijnberg-Williams, B. J., & Laros, J. A. Snijders-Oomen Nonverbal Intelligence Test. SON-R 2.5-7. Manual and research report. Lisse, the Netherlands: Swets & Zeitlinger B.V., 1998.

28. G. van der Steene AB. Wechsler Preschool and Primary Scale of Intelligence- Revised, Dutch version (WPPSI-R), manual. Lisse, the Netherlands: Swets and Zeitlinger BV, 1997.

29. Kort W, Schittekatte M, Dekker PH, et al. WISC-III NL; Wechsler intelligence scale for children, derde Editie NL. Handleiding en verantwoording Londen: Harcourt Assessment 2005.

30. Achenbach TM, Rescorla LA. Manual for the ASEBA PreSchool Age Forms & Profiles. Burlington, VT: ASEBA, 2001.

31. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: ASEBA, 2001.

32. IBM SPSS Statistics for Windows, Version 20.0 [computer program]. Armonk, NY: IBM Corp., 2011.

33. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Academic Press, New York, 1988.

34. Harrell F. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression and Survival Analysis, 2 ed. New York: Springer-Verlag, 2015.

35. Klein-Tasman BP, Janke KM, Luo W, et al. Cognitive and psychosocial phenotype of young children with neurofibromatosis-1. J Int Neuropsychol Soc 2014;20:88-98.

36. Johnson NS, Saal HM, Lovell AM, Schorry EK. Social and emotional problems in children with neurofibromatosis type 1: evidence and proposed interventions. J Pediatr 1999;134:767-772.

37. Martin S, Wolters P, Baldwin A, et al. Social-emotional functioning of children and adolescents with neurofibromatosis type 1 and plexiform neurofibromas: relationships with cognitive, disease, and environmental variables. J Pediatr Psychol 2012;37:713-724.

38. Verhulst FC, Van der Ende, J. Six-year developmental course of internalizing and externalizing problem behaviors. Journal of American academy of child and adolescent psychiatry 1992;31:924-931.

39. Hart KI, Fujiki M, Brinton B, Hart CH. The relationship between social behavior and severity of language impairment. J Speech Lang Hear Res 2004;47:647-662.

40. Henrichs J, Rescorla L, Donkersloot C, et al. Early vocabulary delay and behavioral/emotional problems in early childhood: the generation R study. J Speech Lang Hear Res 2013;56:553-566.

41. Chavira DA, Stein MB, Bailey K, Stein MT. Child anxiety in primary care: prevalent but untreated. Depress Anxiety 2004;20:155-164.

42. van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet 2014;85:318-327.

43. Achenbach TMR, L.A. Manual for the ASEBA Preschool Forms & Profiles. . Burlington, VT: University of Vermont Department of Psychiatry, 2000.

44. Achenbach TMR, L.A. Mental health practitioners' guide for the Achenbach system of empirically basded assessment (ASEBA) (2nd ed.) Burlington, VT: University of Vermont, research center for children, youth & families, 2001.

45. Achenbach T, Rescorla, LA. Multicultural Supplement to the Manual for the ASEBA Preschool Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families, 2010.

46. Plasschaert E, Descheemaeker MJ, Van Eylen L, Noens I, Steyaert J, Legius E. Prevalence of autism spectrum disorder symptoms in children with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2014.

47. Mesman J, Koot HM. Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. J Am Acad Child Adolesc Psychiatry 2001;40:1029-1036.

48. Roza SJ, Hofstra MB, van der Ende J, Verhulst FC. Stable prediction of mood and anxiety disorders based on behavioral and emotional problems in childhood: a 14-year follow-up during childhood, adolescence, and young adulthood. Am J Psychiatry 2003;160:2116-2121.

49. Ollendick TH, King NJ. Diagnosis, assessment, and treatment of internalizing problems in children: the role of longitudinal data. J Consult Clin Psychol 1994;62:918-927.

CHAPTER 4.

Emotional and behavioral problems in children and adolescents with neurofibromatosis type 1

Rietman AB, van der Vaart T, Plasschaert E, Nicholson BA, Oostenbrink R, Krab LC, Descheemaeker MJ, De Wit MCY, Moll HA, Legius E, De Nijs PFA

American Journal of medical genetics part B Neuropsychiatric Genetics 2018;177:319-328

Abstract

To assess emotional and behavioral problems in children and adolescents with neurofibromatosis type 1, parents of 183 individuals aged 10.8 ± 3.1 years (range 6 to 17) completed the Child Behavior Checklist (CBCL). Also, 173 teachers completed the Teacher's Report Form (TRF), and 88 adolescents (children from 11 to 17 years) completed the Youth Self-Report (YSR). According to parental ratings, 32% scored in the clinical range (above the 90th percentile). This percentage was much lower when rated by teachers or adolescents themselves. Scores from all informants on scales for Somatic complaints, Social problems, and Attention problems were significantly different from normative scores. Attentional problems were associated with lower verbal IQ, male gender, younger age, and ADHD-symptoms. Disease-related factors did not predict behavioral problems scores. Substantial emotional and behavioral problems were reported by parents, teachers, and to a lesser extent by adolescents with NF1 themselves. Possibly, a positive illusory bias affects the observation of behavioral problems by adolescents with NF1.

Introduction

Neurofibromatosis type 1 (NF1) is a common genetic disorder, with a birth incidence of at least 1 in 2,700 [1]. NF1 is mainly characterized by various progressive neurocutaneous manifestations, including café-au-lait spots, skinfold freckling, and neurofibromas. The most frequent complications of NF1 in children are deficits in cognition and behavior [2]. Neuropsychological deficits include a lowered average IQ, as well as problems with academic skills, visuospatial skills, social competence, and attention [3]. Up to 75% of NF1 children have learning disabilities and the majority of children need additional support, e.g. special education and/or remedial teaching [4]. Parental behavioral reports using the Child Behavior Checklist (CBCL) tend to reveal problems predominantly in the internalizing domain, encompassing anxiety, depression, social withdrawal, and somatic complaints [5, 6].

So far, assessments of the behavioral phenotype of children with NF1 have mainly focused on reports by proxies [7-9]. The addition of children's perspectives could help guide future consultation. Former studies used small numbers of NF1-patients, whereas larger samples might facilitate the identification of predictors of behavioral problems.

This study aims to (1) describe emotional and behavioral problems in a large group of children with NF1 as identified by parent and teacher reports versus self-reports and (2) identify demographic, cognitive and disease-related factors contributing to these problems.

Method

Procedure

Patients were recruited from the NF1 outpatient clinics of two national referral centers: the Erasmus Medical Center, Sophia Children's Hospital (Rotterdam, the Netherlands), and the Centre for Human Genetics of the University Hospitals of Leuven (Belgium). These were supplemented with baseline data of participants from two randomized controlled trials [10, 11]. When children had more than one evaluation, the most recent one was used. Inclusion criteria for this study were: NF1 diagnosis according to the criteria of the National Institutes of Health [12], age 6 to 18 years, and informed consent from parents and from adolescents aged 12 years and older. For the purpose of this study, patients were included if at least one parent questionnaire (Child Behavior Checklist: CBCL) was completed between 2005 and 2013**.** Exclusion criteria for all children and adolescents

were: segmental NF1, symptomatic CNS pathology (including cerebral tumors or symptomatic optic pathway gliomas requiring treatment), deafness or severely impaired vision, use of anti-epileptic medication, inefficient production/ comprehension of the Dutch language, and an IQ below the range covered by the WISC-III-NL (Total IQ below 48). An additional exclusion criterion for one of the trial groups [10] was the use of stimulant drugs. In total, 183 children and adolescents were included. This study was approved by the Medical Ethical Committee of Erasmus MC, Sophia Children's Hospital and the Medical Ethical Committee (MEC) of the University Hospitals of Leuven. For data of all trial participants informed consent was received and for patients in clinical follow-up, a formal review and waiver of the MEC was given.

Instruments

Parents completed the Child Behavior Checklist to assess emotional and behavioral problems with the CBCL/6-18 (120 items). Teachers completed the Teacher's Report Form (TRF, 120 items) and, as is customary, adolescents from 11 to 17 years old completed the Youth Self-Report (YSR, 119 items)[13, 14]. These three questionnaires contain the same eight 'syndrome scales', enabling cross-informant comparison: Anxious/Depressed, Withdrawn/Depressed, and Somatic complaints (together: Internalizing or emotional problems); Rule-breaking behavior and Aggressive behavior (together: Externalizing or behavioral problems); and Social problems, Thought problems, and Attention problems. All questionnaires consist of a problem section with items rated 0 (never true), 1 (somewhat or sometimes true), or 2 (often or always true). Raw scores are converted to T scores (mean 50, *SD* 10), with higher scores corresponding to more problems. Sum-scores result in three broad-band scales for Internalizing, Externalizing, and Total problems. Test-retest reliability in the Dutch population is sufficient to good for the broad-band scales (Pearson's *r* =0.82- 0.94) and acceptable for the syndrome scales (*r* = 0.72- 0.92)[14]. T scores on the broad-band scales between 59 and 64 (84th to 90th percentile) are considered to fall within a borderline clinical range, whilst T scores of 64 and higher fall within the clinical range. For syndrome scales, these cut-off scores are 65 for the borderline range and 70 for the clinical range (93rd and 97th percentile)[14]. Scores were compared with those of the full normative sample of the Dutch version of the CBCL, TRF, and YSR questionnaires. These norms are from a randomly drawn sample, regarded as representative of the total Dutch population.

Physical disease severity was scored using the Riccardi Scale [15], modified to exclude cognitive aspects of NF1 [11] into Minimal NF1 (patient has no features that compromise health, i.e.

only harmless cosmetic features such as *café au lait* maculae, freckling, and Lisch nodules), Mild NF1 (patient has minor medical complications such as small stature or discrete plexiform neurofibroma), Moderate NF1 (patient has complications that are a significant compromise to health, such as paravertebral neurofibromas or hypertension), and Severe NF1 (medical history with malignancy). After reviewing the data, the severity groups 'moderate' and 'severe' were merged, because only four children were in the 'severe' group.

Intelligence was measured with the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL)[16]. The WISC-III-NL is an intelligence test for children aged 6 to 16 years. The test consists of several subtests resulting in a Total IQ, Verbal IQ, and Performance IQ, with a population mean of 100 and an *SD* of 15.

Participants

Clinical data were prospectively registered by a pediatrician experienced in NF1. Socioeconomic status was determined from highest parental occupation and was divided into low, middle, or high, modified from the Dutch standard occupation classification [17]. Children with an ADHD classification regardless of subtype (inattentive, hyperactive/impulsive or combined) were identified independently from CBCL-scores by a retrospective chart review using DSM-IV criteria.

Statistical analyses

Data were analyzed using SPSS 21. In behavioral rating scales, data are usually non-normally distributed, as is the case in our sample. Therefore, we used nonparametric tests for comparisons (independent samples Mann-Whitney U-tests or independent-samples Kruskal-Wallis tests). Although Table 2 reports T scores to communicate clinically relevant data, all comparisons and regressions in other tables were performed using raw scores. Spearman's ρ correlations were calculated to measure agreement between parent-, teacher-, and self-ratings, with correlations between .10 and .29 representing a small association, .30-.49 a medium association, and above 0.50 a large association.[18] Effect sizes were calculated using Cohen's *d*, with .20 interpreted as a small effect size, .50 as medium, and .80 as large [18]. When comparing scores on syndrome scales with those of the Dutch normative sample of CBCL, TRF, and YSR, the level of significance was adjusted for multiple testing with a Bonferroni correction. Since all three questionnaires contain eight syndrome scales, α was set at .025/(3*8) = .001.

In regression analysis, a two-phase strategy was followed for each of the outcome measures. In phase 1, all separate prediction variables from Table 1 were tested in univariable analyses on those CBCL, TRF, and YSR syndrome scales on which scores were significantly different from the normative sample for all three informants. Since this phase served as an initial, broad selection of predictors, α in phase 1 was set at .10. The final model in phase 2 contained all significant variables from phase 1. Variables shown to be significant contributors in the final model were regarded as the final predictors of CBCL, TRF, and YSR outcomes (α in phase 2 was set at .05; backward elimination procedure).

Results

Patient characteristics

We included 183 children and adolescents, 129 from the Netherlands and 54 from Belgium. Seventy percent of the children (*N*=128) were participants from randomized controlled trials, 24 percent (*N*=44) from the first trial [11], 46 percent (*N*=84) from the second [10], the other thirty percent (*N*=55) were patients from outpatient clinics. General, cognitive, and disease-specific NF1 characteristics are shown in Table 1. Teachers of 173 children (95%) completed the TRF and 88 of these children (48%) completed a YSR (i.e. 90% of those eligible for self-report). As to our knowledge, missing data were due to the fact that some teachers or adolescents did not return the forms that were sent or given to them. The age-range of all children was 6 to 17 years. Thirty-six percent (*n*=66) attended a school for special education. ADHD classifications were present in 53 children (33%), of whom 19 used behavioral medication: 18 used stimulants and one used anti-psychotic medication. Of the children without ADHD classification, one used anti-psychotic medication. The distribution of Total IQ scores was shifted to the left while retaining a Gaussian distribution and ranged from 51 to 125. Not all information from patient records was found to be complete. Particularly information on ADHD, IQ, microdeletion status and parental profession was not routinely collected in the outpatient clinics and were missing in 7-20% of the patients.

Table 1. Characteristics of the Children with NF1

Characteristic	*N* (%)
General characteristics (*N*=183)	
Age at time of CBCL[a]	10.8 (3.1)
Gender	
Male	100/183 (55%)
Female	83/183 (45%)
Socio-Economic Status	
Low	51/148 (34%)
Middle	49/148 (33%)
High	48/148 (32%)
School Type	
Regular	115/181 (64%)
Special	66/181 (36%)
ADHD	
Yes	53/161 (33%)
No	108/161 (67%)
Cognition[a] (*N*=158)	
Total IQ	85 (16)
Verbal IQ	87 (16)
Performance IQ	86 (16)
NF1 Characteristics (*N*=183)	
Mode of Inheritance	
Familial	70/170 (41%)
Sporadic	100/170 (59%)
NF1-Microdeletion	14/159 (9%)
Severity	
Minimal	84/179 (47%)
Mild	33/179 (18%)
Moderate	58/179 (32%)
Severe	4/179 (2%)

Data represented as number/sample size and percentage unless stated otherwise. [a]Mean (SD).

Behavioral problems in a large sample of children and adolescents with NF1

Scores on the CBCL, TRF, and YSR questionnaires are shown in Table 2. Cronbach's alpha's as calculated for the CBCL (116 items; α = .956), the TRF (111 items; α =.933), and the YSR (115 items; α =.924) were excellent, indicating high internal consistency. We found no differences between the groups of data-origin (trial/outpatient clinics, Belgian/Dutch) on syndrome scale scores. Also, scores of the children from the second trial [10], where additional exclusion criteria were applicable, did not differ from scores from the other children. In addition, percentages of ADHD classifications were not different when comparing the children within this trial to children in the other groups (χ^2 (1, *N*= 161)=.672, *p*=.412)). Overall, parents scored behavioral problems in the clinical range more frequently than teachers or children, illustrated by the overall rating on the Total problems Scale, with scores of parent ratings in the clinical range for 58 children (32%), compared to 35 (20%) according to teachers and only six (7%) according to adolescents themselves, as is shown in Figure 1. For comparison of groups, we looked at those individuals (N=81) from whom all three questionnaires (CBCL, TRF, and YSR) were present and found proportions of adolescents scoring in the clinical range that did not differ substantially: 31%, 21%, and 7% respectively. Associations between informants on syndrome scales are all small to medium-sized and comparable to those found in the general population. Associations of parent-teacher ratings range from .25 to .47 in the NF1 group and from .21 to.44 in the normative sample [14]. Associations between parent- and self-ratings range from .17 to .51 for NF1 and from .29 to .53 in the normative sample. Between teacher- and self-ratings, associations range from .004 to .28 for NF1 and from .01 to .36 in the normative sample.

As shown in Table 3, raw scores on most scales differed significantly from those of the normative sample. After adjusting for multiple comparisons, all three informants reported significantly more problems on the broad-band scale for Internalizing problems and on the syndrome scales for Somatic complaints, Social problems, and Attention problems, compared with the normative sample. Effect sizes of parent ratings were generally larger than those of teacher- and self-ratings. Parents reported significant problems, with medium to large effect sizes on four out of eight syndrome scales: Somatic complaints (*d* = .54), Social problems (*d* = 1.19), Thought problems (*d* = .52), Attention problems (*d* = 1.02). According to teacher-ratings, Social problems had a medium effect size (*d* = .67). For self-ratings, Social problems (*d* = .73) had a medium effect size. All other effect sizes were below medium. The lowest scores were on the Rule-breaking behavior scale.

As shown in Table 3, raw scores on most scales differed significantly from those of the normative sample. After adjusting for multiple comparisons, all three informants reported significantly more problems on the broad-band scale for Internalizing problems and on the syndrome scales for Somatic complaints, Social problems, and Attention problems, compared with the normative sample. Effect sizes of parent ratings were generally larger than those of teacher- and self-ratings. Parents reported significant problems, with medium to large effect sizes on four out of eight syndrome scales: Somatic complaints (*d* = .54), Social problems (*d* = 1.19), Thought problems (*d* = .52), Attention problems (*d* = 1.02). According to teacher-ratings, Social problems had a medium effect size (*d* = .67). For self-ratings, Social problems (*d* = .73) had a medium effect size. All other effect sizes were below medium. The lowest scores were on the Rule-breaking behavior scale.

Predictors of emotional and behavioral problems

When comparing disease characteristics of subgroups, there were no differences in scores on broad-band problem scales between children with a familial or sporadic mutation, between children with or without a microdeletion, nor between those with minimal, mild, or moderate/severe disease severity.

Single linear regression analysis (phase 1; Table 4) revealed possible predictors for three selected syndrome scales: Somatic complaints, Social problems, and Attention problems. In multivariable regression analyses (phase 2; Table 5), significant predictors were found for parent- and teacher-rated Attention problems. Models for the other scales identified no significant predictors. Total IQ was not entered in the regression analyses because verbal IQ accounted for the significant contribution of total IQ.

Parent-reported Attention problems were predicted by ADHD and lower verbal IQ. Teacher-reported Attention problems were predicted by younger age, male gender, ADHD, and lower verbal IQ.

Table 2. Parent-, teacher-, and self-reported T scores for emotional and behavioral problems

	Parents (CBCL; *N*=183)				**Teachers** (TRF; *N*=173)				**Self-Report** (YSR; *N*=88)			
Emotional-Behavioral Domain	*M*	*(SD)*	*BCR (%)*	*CR (%)*	*M*	*(SD)*	*BCR (%)*	*CR (%)*	*M*	*(SD)*	*BCR (%)*	*CR (%)*
Problem Scales												
Internalizing problems	56.1	(10.9)	12	26	56.0	(10.0)	17	10	54.3	(9.9)	22	16
Externalizing problems	53.4	(11.0)	10	22	52.0	(8.4)	12	10	48.1	(9.1)	11	5
Total problems	58.3	(10.3)	14	32	56.2	(7.5)	9	20	52.7	(9.3)	25	7
Syndrome Scales												
Anxious-depressed	56.2	(8.5)	10	8	57.5	(7.8)	9	10	55.6	(6.2)	7	1
Withdrawn-depressed	58.1	(8.7)	10	13	56.7	(6.3)	10	3	55.9	(5.7)	9	1
Somatic complaints	59.1	(8.1)	9	14	55.9	(7.4)	9	5	57.5	(7.3)	14	7
Social problems	62.7	(8.3)	21	20	60.8	(7.9)	14	15	58.9	(7.2)	22	5
Thought problems	59.0	(8.5)	13	16	55.6	(7.0)	6	5	55.4	(5.8)	3	3
Attention problems	62.2	(8.4)	22	13	55.9	(5.0)	5	1	57.2	(7.8)	16	3
Rule-breaking behavior	54.6	(5.4)	4	3	52.9	(4.8)	3	1	52.8	(3.6)	0	0
Aggressive behavior	57.7	(8.6)	11	11	55.4	(6.1)	7	2	53.3	(5.6)	6	2

BCR/CR: Percentage of scores in borderline clinical range/clinical range. In normative sample, $M = 50$, $SD = 10$, higher scores reflect more problems.

Table 3. Parent-, teacher-, and self-reported raw scores and effect sizes for emotional and behavioral problems when comparing children with NF1 with a normative sample

	Parents (CBCL)				Teachers (TRF)				Self-Report (YSR)			
Emotional-Behavioral Domain	Norm (*N* = 1710)	NF1 (*N* = 183)	Effect Size	*p*	Norm (*N* = 1139)	NF1 (*N* = 173)	Effect Size	*p*	Norm (*N* = 862)	NF1 (*N* = 88)	Effect Size	*p*
Problem Scales												
Internalizing problems	6.9 (6.0)	9.7 (8.3)	0.39	<.001*	5.4 (5.8)	7.8 (7.1)	0.37	<.001*	10.2 (7.1)	13.1 (7.5)[a]	0.40	<.001*
Externalizing problems	6.7 (6.4)	9.4 (8.2)	0.36	<.001*	4.4 (6.8)	4.6 (6.7)	0.03	.56	9.3 (6.3)	8.5 (5.9)[a]	-0.12	.30
Total problems	25.2 (17.9)	40.6 (25.6)	0.70	<.001*	21.1 (20.2)	30.6 (21.1)	0.46	<.001*	35.0 (18.2)	41.3 (18.8)[a]	0.34	.002
Syndrome Scales												
Anxious-depressed	3.2 (3.1)	4.0 (4.1)	0.22	.04	2.9 (3.4)	4.2 (4.3)	0.33	<.001*	4.2 (3.7)	5.2 (3.7)	0.27	.006
Withdrawn-depressed	2.2 (2.3)	2.8 (3.0)	0.26	.03	2.1 (2.5)	2.5 (2.6)	0.17	.02	3.0 (2.3)	3.7 (2.3)	0.32	.003
Somatic complaints	1.6 (2.1)	2.9 (2.9)	**0.54**	<.001*	0.5 (1.3)	1.2 (1.9)	0.42	<.001*	3.0 (2.6)	4.2 (3.0)	0.45	<.001*
Social problems	2.2 (2.4)	5.8 (3.5)	**1.19**	<.001*	1.7 (2.5)	3.7 (3.3)	**0.67**	<.001*	3.2 (2.4)	5.2 (3.1)	**0.70**	<.001*
Thought problems	2.0 (2.3)	3.5 (3.5)	**0.52**	<.001*	0.5 (1.2)	1.2 (2.0)	0.44	<.001*	3.2 (2.8)	4.1 (3.1)	0.30	.009
Attention problems	3.9 (3.3)	7.7 (4.0)	**1.02**	<.001*	8.4 (8.8)	12.2 (8.8)	0.44	<.001*	5.1 (3.0)	6.3 (3.3)	0.38	.001*
Rule-breaking behavior	2.1 (2.5)	2.1 (2.4)	0.01	.79	1.3 (2.2)	0.9 (1.7)	-0.19	.02	4.0 (3.1)	3.0 (2.2)	-0.38	.008
Aggressive behavior	4.6 (4.6)	7.2 (6.4)	0.47	<.001*	3.1 (5.1)	3.7 (5.4)	0.11	.13	5.3 (3.9)	5.5 (4.3)	0.06	.79

Effect size represented with Cohen's *d*. All other data are presented as Mean (*SD*). Higher raw scores indicate more problems.

[a]*N* = 90. *=significant after Bonferroni correction with $\alpha = .025/(3*8) = .001$. Medium to large effect sizes in **bold** print.

Table 4. Prediction of Scores on Selected Syndrome Scales of Parent- (CBCL), Teacher- (TRF) and Self- Reported (YSR) Emotional and Behavioral Problems by Separate Prediction Variables Data

Predictor Variables	*N*	CBCL Somatic Complaints		CBCL Social Problems		CBCL Attention Problems		TRF Somatic Complaints		TRF Social Problems		TRF Attention Problems		YSR Somatic Complaints		YSR Social Problems		YSR Attention Problems	
General Characteristics																			
	N	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2	*β*	R^2
Age	183	.126$^{\#}$	.016	.069	.005	-.031	.001	.068	.005	-.012	.000	-.149$^{\#}$	.022	-.211$^{\#}$	.045	.035	.001	.003	.000
Gender	183	.070	.005	-.127$^{\#}$	.016	-.151*	.023	.008	.000	-.081	.007	-.322***	.104	-.048	.002	.101	.010	.096	.009
SES	148	-.033	.001	-.018	.000	-.065	.004	-.064	.004	-.125	.125	-.133	.018	.132	.017	.124	.015	.197$^{\#}$	.039
School type	181	.028	.001	.041	.002	.220**	.048	.036	.001	.061	.004	.078	.006	-.109	.012	-.096	.009	-.100	.010
ADHD	161	.069	.005	.078	.006	.276***	.076	.085	.007	.070	.005	.305***	.093	.045	.002	.146	.021	.092	.009
Cognition																			
Total IQ	158	-.070	.005	-.088	.008	-.183*	.034	.027	.001	-.071	.005	-.152$^{\#}$	.023	.111	.012	.030	.001	.072	.005
Verbal IQ	158	-.058	.003	-.154$^{\#}$	.024	-.229**	.052	-.002	.000	-.095	.009	-.183*	.033	.176	.031	.076	.006	.083	.007
Performance IQ	158	-.079	.006	-.011	.000	-.101	.010	.041	.002	-.030	.001	-.082	.007	.009	.000	-.034	.001	.024	.001
NF1 Characteristics																			
Familial	170	-.007	.000	-.074	.006	-.110	.012	.074	.006	-.011	.000	.004	.000	.096	.009	.137	.019	-.041	.002
NF1-Microdeletion	148	.030	.001	.047	.002	-.008	.000	.015	.000	.003	.000	-.049	.002	-.075	.006	-.125	.016	.003	.000
Severity	179	-.046	.002	.069	.005	.060	.004	-.046	.002	.072	.005	-.074	.006	-.140	.019	-.066	.004	-.082	.007

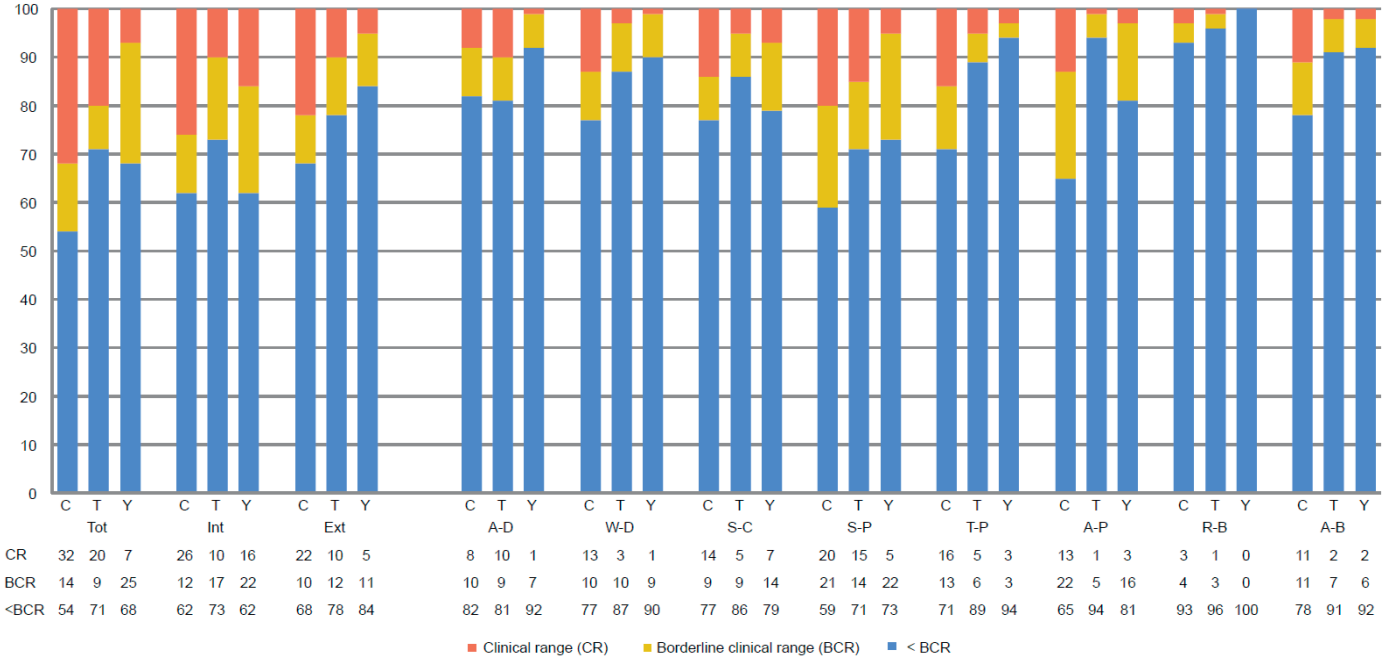
Represented as standardized beta coefficient (*β*) and unadjusted R^2. *N* represents sample size in CBCL. $^{\#}p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Table 5. Multivariable Backward Regression Analyses showing significant predictors of scores on syndrome scales for Somatic complaints, Social problems, and Attention problems from CBCL (parent rating), TRF (teacher rating), and YSR (adolescent self-rating)

Predictor and Outcome Variables	*df*	*F*	R^2	Adjusted R^2	Constant	Unstandardized coefficient *b*	*SE*	Standardized coefficient *β*
CBCL								
Social problems								
Model 1	157	2.69	.03	.02	9.61			
Gender						-.71	.57	-.10
Verbal IQ						-.03	.02	-.15
Model 2	157	3.81	.02	.02	8.69			
Verbal IQ						-.03	.02	-.15
Attention problems								
Model 1	137	4.75**	.13	.10	12.11			
Gender						-.56	.68	-.07
School type						.16	.84	.02
ADHD						2.11	.72	.24**
Verbal IQ						-.05	.03	-.20*
Model 3	137	9.21***	.12	.11	11.81			
ADHD						2.22	.70	.26**
Verbal IQ						-.05	.02	-.22**
TRF								
Attention problems								
Model 1	126	11.30***	.27	.25	35.14			
Age						-.59	.25	-.19*
Gender						-5.85	1.45	-.32***
ADHD						5.02	1.55	.26**
Verbal IQ						-.10	.04	-.19**

*p <.05. **p <.01. ***p <.001.

Figure 1. The Prevalence of Emotional and Behavioral Problems in Children with NF1 according to Parent-, Teacher- and Self-Reports



C: Child Behavior Checklist (CBCL); T: Teacher Report Form (TRF); Y: Youth Self Report (YSR). Tot: Total problems scale; Int: Internalizing problems scale; Ext: Externalizing problems scale; A-D: anxious depresses; W-D: Withdrawn/Depressed; S-C: Somatic Complaints; S-P: Social Problems; T-P: Thought Problems; A-P: Attention Problems; R-B: Rule-Breaking Behavior; A-B: Aggressive Behavior. Numbers are percentages of children; C BCL: *N*= 183; TRF: *N*= 173 *N*= 8

Discussion

In this study, not only parent- and teacher-ratings in children with NF1 were taken into account, but also adolescent's self-reports of emotional and behavioral problems. Parents, teachers, and adolescents reported significantly elevated scores for emotional and behavioral problems in a large group of children and adolescents with NF1. Children and adolescents with NF1 differed from children and adolescents from a normative sample on most of the broad-band scales and syndrome scales. In parent ratings, a high percentage of children (32%) displayed clinically significant problems. Teachers and adolescents reported fewer problems in the clinical range. Parents reported more severe problem behaviors over a wider range of areas than teachers, and teachers reported more problem behaviors than adolescents themselves.

Adolescents with NF1 reported fewer behavioral difficulties than their parents, whereas self-reports of adolescents from reference populations in various countries report *more* problems than their parents [19]. Notably, even ADHD was *not* predictive of self-rated attention problems. The tendency towards a more positive self-report seen in our study is reminiscent of the pattern seen in children with NF1 reporting rather positively on their academic performance compared to objective measures [20] or on their quality of life compared to their parents [21]. In children with ADHD, children with learning disabilities [22], and in children with NF1[20], this 'positive illusory bias', serving as a self-protective mechanism, is regarded a possible explanation for these discrepancies.

In the general population, the agreement between informants is typically modest [23, 24]. Discrepancies between informants may be determinants of poor outcome. For instance, a CBCL-YSR discrepancy on the rating of attention problems in a clinical sample predicted disciplinary problems at school some four years later [23]. Since this discrepancy is clearly present in this group of adolescents with NF1, caregivers should pay attention to the views of both parents and adolescents. Although the agreement between parents, teachers, and adolescents can be low, all different perspectives contribute to a more complete view of children and their problems. Also, the psychological treatment of adolescents with parent and teacher-rated emotional and behavioral problems will be different when the adolescents themselves do not agree with their parent's and teacher's reports. In that case, the motivation for treatment may need to be addressed before starting treatment. Creating awareness for another's perception of behavior could be an important focus in therapy.

Children with NF1 differed significantly from a normative sample on most broad-band and syndrome scales. However, not all of these differences had a large effect size. There was a strong agreement between all informants regarding high scores on the Social problems scale. This underlines the presence and severity of social problems in children and adolescents with NF1. Previous research in smaller groups [7, 9, 25] reported the social problems and the lack of social skills in children with NF1, particularly in those with comorbid ADHD [9] or ASD [26-28]. Unfortunately, we did not find any significant predictors of these social problems. Other studies found an elevated risk of poor social functioning [9] and social competence problems in children with elevated ADHD symptoms [28]. Possibly, our sample did not show this effect due to a lower severity of ADHD symptoms as a result of the exclusion of children with ADHD using stimulant medication in one of the trials [10], containing 46% of the children. A different explanation for this decreased association of social problems and ADHD in NF1 could be that the NF1 mutation itself is responsible for limitations in social learning, next to other factors that impact on social learning, such as ADHD and ASD [29].

ADHD and a lower verbal IQ independently predicted more parent- and teacher-rated attentional problems. Young age and male gender were additional independent predictors of teacher-rated attentional problems. The association between ADHD, male gender and attentional problems is not new, in this respect, children with NF1 do not differ from children in the general population. Males, in general, are more likely to meet the criteria for ADHD, confirming this association between gender and attentional problems [30]. Although the prevalence of attentional problems generally does not decrease with age in children in this age range [30], this is the case in our group. The association between lower verbal IQ and attentional problems is of interest, as it adds new evidence to the suggested link between verbal IQ and ADHD in NF1. A recent study suggested a link between verbal IQ and both ADHD and ASD symptoms [31]. In our study, we did not assess ASD symptoms but we did find a high level of social problems. Although in the current study, the association between verbal IQ and social problems did not reach significance, the triad of social, attentional, and verbal problems may be a point of concern in children and adolescents with NF1 and warrants further investigation. In NF1, male gender, ADHD, young age and low verbal IQ should not only be regarded as predictors of attentional problems at school but also as risk factors for developing these problems.

In none of the final regression models, disease-related factors such as disease severity, NF1-microdeletion status, and familial inheritance were significant predictors of behavioral outcome.

Although disease characteristics such as severity of NF1 do have an effect on the perceived quality of life in adults [32], this is not the case for behavioral problems in the current group of children and adolescents. Since NF1 is a progressive disorder and somatic problems tend to increase during life, the relationship between disease characteristics, behavioral functioning, and quality of life might not yet be established in or noticed by children. A study using the BASC-2 parent questionnaire [33] did find an association between disease severity and internalizing problems in 50 children. Differences between the instruments used to measure disease severity, between the questionnaire items, or between the samples could be reasons why this association was found in the Martin et al. study and not in the study reported here. Future studies could benefit from using more comparable instruments for disease severity in NF1.

There are several strengths and limitations to this study. In NF1, studies in large groups of patients are rare. We succeeded in gathering data on 183 children between 6 and 17 years old over a period of eight years. Since all children visited a university hospital, there is a risk of an academic selection bias, possibly including children with more severe problems. However, both centers are national referral centers in two geographically small countries and all children were offered a periodic follow-up. Since seventy percent of the children were recruited for randomized controlled trials, there is a possibility for ascertainment bias. However, these children did not differ in their behavioral scores from children in clinical follow-up. Although for a subgroup of children (46%), the use of stimulant medication was an exclusion criterion, the proportion of children with ADHD did not differ between the children in this subgroup and the other children in our study, nor was there a difference between this subgroup and the total group. Nevertheless, this selection could have biased the sample towards a less severe behavioral phenotype, limiting the generalizability of the results.

Not all data in this study were complete. For instance, information on intelligence, NF1-microdeletion status, and parental profession was not routinely collected in the group of outpatient children. However, the group with missing data did not differ significantly from the group that had complete data on any of the behavioral scale scores.

Conclusion

This study shows that in parent-ratings, almost one-third of the children with NF1 have severe emotional and behavioral problems. Most of these problems are in the internalizing domain but

adolescents themselves are less likely to report these problems. This might hinder the identification of these problems, especially for caregivers that have a less intimate relationship with the child. Whilst teachers and adolescents themselves report fewer problems than parents do, they also report different problems from ecologically different perspectives. Problem behavior might be tackled more effectively if multiple views are taken into account. Groups at risk for developing these problems are children with NF1 and a lower verbal IQ, boys, younger children (primary school age), and children with ADHD-symptoms.

NF1 clearly predisposes to behavioral problems, and this is most likely not associated with the physical severity of the disease. Although animal studies have shed light on the molecular and cellular mechanisms underlying cognitive problems [34], the way these mechanisms lead to emotional and behavioral problems remains unclear. In the follow-up of children and adolescents with NF1, one should screen for a wide range of emotional and behavioral problems, using multiple informants. Whenever these screenings are positive, referral to mental health professionals is recommended.

Acknowledgements

The authors thank all the children and families for participating in this trial. We thank Badies Manai for his assistance in data collection and management, and Lisbeth Utens for valuable discussions. We also thank clinicians throughout the Netherlands and Belgium for referring patients, and the Dutch (Neurofibromatose Vereniging Nederland) and Belgian (NF Kontakt) patients organizations for their ongoing support.

References

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

2. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81-88.

3. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

4. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008;23:1002-1010.

5. Graf A, Landolt MA, Mori AC, Boltshauser E. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. J Pediatr 2006;149:348-353.

6. Johnson NS, Saal HM, Lovell AM, Schorry EK. Social and emotional problems in children with neurofibromatosis type 1: evidence and proposed interventions. J Pediatr 1999;134:767-772.

7. Dilts CV, Carey JC, Kircher JC, et al. Children and adolescents with neurofibromatosis 1: a behavioral phenotype. J Dev Behav Pediatr 1996;17:229-239.

8. Descheemaeker MJ, Ghesquiere P, Symons H, Fryns JP, Legius E. Behavioural, academic and neuropsychological profile of normally gifted Neurofibromatosis type 1 children. J Intellect Disabil Res 2005;49:33-46.

9. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-563.

10. van der Vaart T, Plasschaert E, Rietman AB, et al. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol 2013;12:1076-1083.

11. Krab LC, de Goede-Bolder A, Aarsen FK, et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008;300:287-294.

12. NIH nioh. Neurofibromatosis. NIH Consens Statement 1987 Jul 13-15. 1987;6:1-19.

13. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: ASEBA, 2001.

14. Verhulst F, Van der Ende, J. Handleiding ASEBA: Vragenlijsten voor Leeftijden 6 t/m 18 jaar. Rotterdam: ASEBA Nederland, 2013.

15. Riccardi VM. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. 2nd ed. Baltimore, MD: Johns Hopkins University Press, 1992.

16. Kort W, Schittekatte M, Dekker PH, et al. WISC-III NL; Wechsler intelligence scale for children, derde Editie NL. Handleiding en verantwoording Londen: Harcourt Assessment 2005.

17. Division of Social and Environmental statistics; Section Development and Support; Dutch Central Bureau of Statistics C. Standardized Classification of Professions 1992. Voorburg/Heerlen, the Netherlands: Central Bureau of Statistics, the Netherlands, 2001

18. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Academic Press, New York, 1988.

19. Achenbach TM, Becker A, Dopfner M, et al. Multicultural assessment of child and adolescent psychopathology with ASEBA and SDQ instruments: research findings, applications, and future directions. J Child Psychol Psychiatry 2008;49:251-275.

20. Barton B, North K. The self-concept of children and adolescents with neurofibromatosis type 1. Child Care Health Dev 2007;33:401-408.

21. Krab LC, Oostenbrink R, de Goede-Bolder A, Aarsen FK, Elgersma Y, Moll HA. Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior. J Pediatr 2009;154:420-425, 425 e421.

22. Heath NL, Glen T. Positive illusory bias and the self-protective hypothesis in children with learning disabilities. J Clin Child Adolesc Psychol 2005;34:272-281.

23. Ferdinand RF, van der Ende J, Verhulst FC. Prognostic value of parent-adolescent disagreement in a referred sample. Eur Child Adolesc Psychiatry 2006;15:156-162.

24. Stanger C, Lewis M. Agreement among parents, teachers, and children on internalizing and externalizing behavior problems. J Clin Child Psychol 1993;22:107-115.

25. Garg S, Plasschaert E, Descheemaeker MJ, et al. Autism Spectrum Disorder Profile in Neurofibromatosis Type I. J Autism Dev Disord 2014.

26. Garg S, Lehtonen A, Huson SM, et al. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. Dev Med Child Neurol 2013;55:139-145.

27. Plasschaert E, Descheemaeker MJ, Van Eylen L, Noens I, Steyaert J, Legius E. Prevalence of Autism Spectrum Disorder symptoms in children with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2015;168B:72-80.

28. Walsh KS, Velez JI, Kardel PG, et al. Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1. Dev Med Child Neurol 2013;55:131-138.

29. Morris SM, Acosta MT, Garg S, et al. Disease Burden and Symptom Structure of Autism in Neurofibromatosis Type 1: A Study of the International NF1-ASD Consortium Team (INFACT). JAMA Psychiatry 2016;73:1276-1284.

30. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 2012;9:490-499.

31. Sokolova E, Oerlemans AM, Rommelse NN, et al. A Causal and Mediation Analysis of the Comorbidity Between Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). J Autism Dev Disord 2017;47:1595-1604.

32. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421-1425.

33. Martin S, Wolters P, Baldwin A, et al. Social-emotional functioning of children and adolescents with neurofibromatosis type 1 and plexiform neurofibromas: relationships with cognitive, disease, and environmental variables. J Pediatr Psychol 2012;37:713-724.

34. Diggs-Andrews KA, Gutmann DH. Modeling cognitive dysfunction in neurofibromatosis-1. Trends Neurosci 2013;36:237-247.

CHAPTER 5.

Predictors of mental quality of life of adolescents and young adults with neurofibromatosis type 1

Rietman AB, Oostenbrink R, Plasschaert E, Descheemaeker MJ, de Wit MCY, ten Hoopen L, de Nijs PFA, Legius E, Moll HA

Submitted 2019

This paper has been submitted, but is excluded from the digital version of this thesis because it has not yet been published.

-

CHAPTER 6.

Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial

van der Vaart T, Plasschaert E, Rietman AB, Renard M, Oostenbrink R, Vogels A, de Wit MC, Descheemaeker MJ, Vergouwe Y, Catsman-Berrevoets CE, Legius E, Elgersma Y, Moll HA

The Lancet Neurology 2013;12:1076-1083

Summary

Background

Neurofibromatosis type 1 is a common genetic disorder characterised by neurocutaneous manifestations and cognitive and behavioural problems. Statins were shown to reduce analogous learning deficits in a mouse model of the disease, but a short-term trial in humans was inconclusive. We aimed to assess the use of simvastatin for the improvement of cognitive and behavioural deficits in children with neurofibromatosis type 1 for 12 months.

Methods

In this randomised, double-masked, placebo-controlled trial, we recruited children with genetically confirmed neurofibromatosis type 1 aged 8–16 years from two national referral centres in the Netherlands and Belgium. Those with symptomatic CNS abnormalities or on neurotropic medication, including stimulants, were excluded. Eligible patients were randomly assigned (1:1) via a computer-generated, permuted-block list to simvastatin (10 mg per day in month 1, 20 mg per day in month 2, and 20–40 mg per day in months 3–12) or placebo for 12 months. Investigators, participants, and parents were masked to treatment assignment. Primary outcome measures were full-scale intelligence (Wechsler intelligence scale for children), attention problems (child behaviour checklist, parent-rated [CBCL]), and internalising behavioural problems (CBCL). We did intention-to-treat analyses (of all patients who had outcome data) using linear regression of the 12 month outcome scores, adjusted for baseline performance. This trial is registered with the Netherlands Trial Register, number NTR2150.

Findings

We randomly assigned 84 children to a treatment group (43 to simvastatin, 41 to placebo) between March 9, 2010, and March 6, 2012. We did not assess outcomes in two patients in the placebo group because they needed additional drug therapy. Simvastatin for 12 months had no effect on full-scale intelligence (treatment effect compared with placebo –1.3 IQ points [95% CI –3.8 to 1.3]; p=0.33), attention problems (–1.6 T-score points [–4.3 to 1.0]; p=0.23), and internalising behavioural problems (–0.1 T-score points [–3.3 to 3.1]; p=0.96). 38 (88%) of 43 patients on simvastatin and 39 (95%) of 41 patients on placebo reported adverse events, which were serious in two and four patients, respectively.

Interpretation

12 month simvastatin treatment did not ameliorate cognitive deficits or behavioural problems in children with neurofibromatosis type 1. The use of 20–40 mg simvastatin per day for cognitive enhancement in children with neurofibromatosis type 1 is not recommended.

Introduction

Neurofibromatosis type 1 is a common autosomal-dominant disorder, with a prevalence of 1 in every 2500–3000 births.[1] It is caused by loss-of-function mutations in the NF1 gene, which encodes neurofibromin, a negative regulator of rat-sarcoma viral oncogene homologue (Ras). Neurofibromatosis type 1 is characterised by cutaneous café-au-lait spots, neurofibromas, and cognitive and behavioural problems.[2] Up to 80% of children aged 6–18 years with neurofibromatosis type 1 present with moderate to severe impairment in one or more areas of cognitive functioning, and 40% attend special education.[3,4] Moreover, 30–40% of children with neurofibromatosis type 1 fulfil criteria for attention deficit hyperactivity disorder and up to 60% have problems with executive functioning.[3,5] The average intelligence quotient (IQ) is 10–15 points lower in these children than in population or sibling control groups.[3,6] Parents of children with neurofibromatosis type 1 frequently report difficulties in their child's social daily life activities and a high rate of internalising behavioural problems, such as anxiety or mood disorders.[7] Taken together, cognitive and behavioural deficits lead to lower academic achievement and loss of quality of life,[4,8,9] persisting into adulthood.[10] The learning and attention deficits noted in patients with neurofibromatosis type 1 are reported in the *Nf1*$^{+/-}$ mouse model,[11–13] accompanied by a decrease in synaptic plasticity.[11–13] These animal studies have shown that the plasticity and behavioural deficits are reversed by reducing Ras activity.[11,14] Ras activity requires farnesylation, which allows Ras to anchor to the plasma membrane where it can be activated by growth-factor receptors and their adaptor proteins. Since cholesterol is an obligate precursor of farnesyl, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase have been suggested as a potential therapy for neurofibromatosis type 1. Indeed, lovastatin normalised Ras activity, rescued synaptic plasticity deficits, and restored learning and attention deficits in the *Nf1*$^{+/-}$ mouse model.[14] Results of a small, open-label, single-arm study of lovastatin in children with neurofibromatosis type 1 suggested that lovastatin improved memory and attention, and normalised default network functional connectivity measured with resting state functional MRI.[15,16]

However, lovastatin is not approved or marketed in many parts of the world, including the European Union. The closest approved alternative, simvastatin, is similar in structure, pharmacokinetics, and blood–brain barrier permeability. Moreover, simvastatin is a slightly more potent inhibitor of HMG-CoA reductase and is better at reducing HMG-CoA reductase activity in

neurons than is lovastatin.[17,18] Although findings of a randomised controlled trial reporting the short-term effect of simvastatin in children with neurofibromatosis type 1 showed no effect after 12 weeks on a set of primary outcome measures,[6] a significant improvement was reported for a secondary outcome measure, the object assembly subtask of the Dutch translation of the third edition of the Wechsler intelligence scale for children (WISC-III-NL).[6]

Although this trial had an overall negative outcome, it had some limitations that might have affected its results: children on stimulant- medication were not excluded, and 12 week treatment was short, with only 4 weeks at the highest target dose. A longer treatment duration would have allowed the assessment of the effects on global cognitive functioning, daily life functioning, and behaviour, and might have been necessary to show clinical benefits.

Given the large amount of safety data in children[6,19] and worldwide marketing authorisation of simvastatin, we aimed to improve upon the limitations of this previous trial by assessing the use of simvastatin for the treatment of cognitive and behavioural deficits in children with neurofibromatosis type 1 for 12 months.

Methods

Study design and participants

We undertook this randomised, parallel-group, placebo-controlled trial in two national referral centres: Erasmus MC (Rotterdam, Netherlands) and UZ Leuven (Leuven, Belgium). We screened patients aged 8–16 years with genetically confirmed neurofibromatosis type 1 for eligibility. Genetic counselling and testing for neurofibromatosis type 1 is part of routine care and was done independently of this trial. The rationale for genetic confirmation was the substantial overlap in phenotypes between neurofibromatosis type 1 and related disorders (e.g., Legius syndrome).[20]

Exclusion criteria were: use of neurotropic medication, including stimulant, anti- psychotic, antiepileptic, antianxiety, and antidepressant drugs, or current simvastatin use; symptomatic CNS abnormalities; insufficient comprehension of the Dutch language; severely impaired vision or deafness; segmental neurofibromatosis type 1; or an IQ below 48.

We obtained informed oral and written consent from parents and assent from children of 12 years and older. Local and national institutional review boards approved the protocol. The trial was done in agreement with the Declaration of Helsinki (version 2008) and Good Clinical Practice guidelines.

Randomisation and masking

Eligible patients were randomly assigned (1:1) by the local hospital pharmacist to simvastatin or matched placebo according to computer-generated, permuted block randomisation lists (ten participants per block, stratified by centre) that were provided by the Department of Biostatistics, Erasmus MC, with medication numbers in the order of enrolment. All investigators, participants, and their parents were masked to treatment allocation. We achieved blinding by using capsules of identical colour, shape, size, weight, smell, and taste.

Procedures

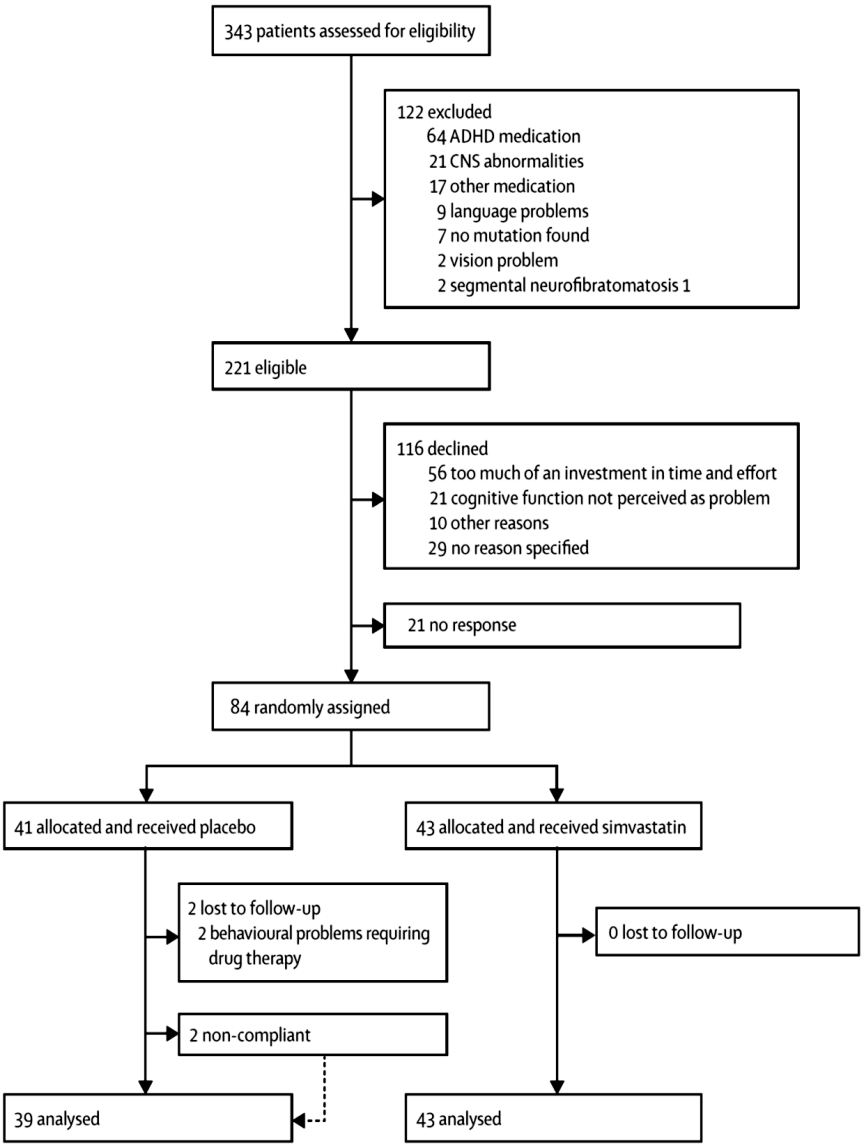
Participants took 10 mg per day of simvastatin or matched placebo once daily in the morning during the first month and 20 mg per day once daily in the morning during the second month. During months 3–12, dosing was fixed at 20 mg per day for children aged 12 years and younger and 40 mg per day for adolescents older than 12 years. We assessed efficacy outcome measures at baseline and at the end of month 12 of treatment. Since no standard measure exists to assess improvement of cognition in patients with neurofibromatosis type 1, we included a broad range of validated tests and questionnaires that are sensitive to the cognitive and behavioural deficits in this group of patients. Outcome measures included constructs that were similar to those that improved in mouse models receiving statins:[14] visual-spatial memory and attention; improvements in daily life behavioural problems rated by parents; and global cognitive functioning. We used three primary outcome measures that are relevant to daily life functioning and academic achievement: full-scale intelligence (WISC-III-NL),[4,6] parent-reported attention problems (child behaviour checklist [CBCL][21]), and parent-reported internalising behavioural problems (CBCL). The attention problems scale of the CBCL consists of items screening for problems in directing and sustaining attention, controlling impulsivity, and hyperactivity. Secondary outcomes were visual-spatial memory (Rey complex figure test–delayed recall),[6] attention (Stroop colour–word interference test),[6] teacher-reported school performance (teacher report form),[21] parent-reported psychosocial quality of life (child health questionnaire–parent form 50 [CHQ-PF50]),[9] patient-reported internalising behavioural problems (youth self-report [YSR] form, completed by patients aged ≥11 years),[21] and fine motor coordination (grooved pegboard test).[8] All neuropsychological tests were developed for children and were written or presented in Dutch. For most outcome measures, we used age-standardised scores. The mean average IQ for the general population is 100 (SD 15), with higher IQ WISC-III-NL test scores indicating higher intelligence.

For CBCL and YSR, data were represented as T scores, with a mean average of 50 and an SD of 10 in the general population, with higher scores indicative of more problems. The Rey complex figure test (for which a higher score suggests a better visual-spatial memory) and CHQ-PF50 (for which a higher score suggests a better quality of life) are presented using Z scores, with 0 representing the mean for the normal sample with an SD of 1. Teacher-reported school performance was calculated on a scale from 2 to 10, by summation of 5-point scores on topics of language and arithmetic, in which higher scores were given for greater ability in each area. For teacher-reported school performance, Stroop colour–word test (for which a lower score suggests better attention), and grooved pegboard test (for which a lower score suggests better fine motor coordination), raw scores were used, since no appropriate normal groups are available for the entire age range. Measurements taken before and after administration of study drug were done by the same neuropsychologist (either ABR or EP). Adverse events and study compliance were monitored by monthly telephone contact and by visits to the outpatient clinic at baseline and at 1, 3, 6, 9, and 12 months. Adverse events were classified according to WHO adverse reaction terminology and graded according to the National Cancer Institute common terminology criteria for adverse events. Blood was drawn at baseline and at 1, 6, 9, and 12 months to measure: alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase to screen for laboratory adverse events; and total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides to assess lower limits of lipid concentrations and to monitor compliance. Further details on procedures are presented in the appendix.

Statistical analysis

We used data from the intention-to-treat population—which consisted of all participants with outcome data—for all primary and secondary analyses, without imputation of missing values. Data from all patients were used for safety analyses—even those without efficacy outcome data. We analysed primary and secondary outcome measures using linear regression for the effect of treatment group on the score at 12 months, adjusted for baseline performance in the bivariable analysis and adjusted for baseline performance, age, and sex in the multivariable analysis.

Figure 1. Trial profile



ADHD = attention deficit hyperactivity disorder

The cut-off level for significance was set at $p<0.05$, ignoring multiple testing. We analysed lipid blood concentrations using the generalised linear mixed model procedure with the interaction of time and treatment as the variable of interest. Sample size calculation suggested that inclusion of 84 participants (85% power; $\alpha=0.05$) would be sufficient to detect a clinically relevant treatment effect of

7.5 full-scale intelligence points (0.5 SD), adjusted for baseline performance, and an increase or decrease of 5 T-score points (SD 0.5) for attention problems and internalising behavioural problems. Inclusion of 84 participants would lead to greater than 80% power on the co-primary outcome measures of attention problems and internalising behavioural problems. Because of low inclusion rates, the protocol was amended from 90% power and 106 participants to 85% power and 84 participants in the second recruitment year, without outcome knowledge and with approval from review boards. We planned the analysis before unmasking according to the study protocol. All data were analysed using IBM SPSS Statistics for Windows (version 20.0).

This trial is registered with the Netherlands Trial Register, number NTR2150.

Role of the funding sources

The sponsors of the study had no role in the conception and design of the trial, the collection, analysis, and interpretation of the data, the writing of the manuscript, or the decision to publish the results. All authors had full access to all of the data in the study, and EL, YE, and HAM had final responsibility for the decision to submit for publication.

For the study protocol see http://www.erasmusmc.nl/nf1-simcoda

Results

We screened 343 patients for eligibility, of whom 221 were eligible. Between March 9, 2010, and March 6, 2012, we obtained informed consent from 84 patients or their parents. They were randomly assigned to 12 months of treatment with simvastatin (n=43) or placebo (n=41). Two patients in the placebo group were lost to follow-up before outcome could be assessed because they had behavioural problems that required drug therapy. Two participants in the placebo group discontinued study medication, but were available for outcome assessment (figure 1). Median compliance per patient was 96% (IQR 93–100), measured by counting returned capsules. Baseline demographic and disease characteristics were generally balanced between both treatment groups, although more patients in the simvastatin group were male than in the placebo group (table 1). At baseline, average full-scale intelligence was 83.3 points (SD 15.6) and 46 (55%) participants had attention problems scored on the CBCL of more than 1 SD above the mean of the general population. Median age was 11.5 years (range 7.9–16.0). 12 months of simvastatin had no significant effect on full-scale intelligence (treatment effect –1·3 IQ points

Table 1. Baseline characteristics

	Simvastatin (n= 43)	Placebo (n= 41)
Age, years	11·1 (9·2 – 13·0)	11·8 (10·2 – 14·7)
Male sex	26 (61%)	13 (32%)
Full-scale intelligence (WISC-III-NL)*	83·8 (16·1)	82·7 (15·3)
Attention problems (CBCL), *T*-score†	61·1 (8·9)	62·8 (8·3)
Internalizing behavioural problems (CBCL), *T*-score†	55·2 (10·7)	56·7 (10·1)
NF1 disease severity‡		
Minimal	18 (42%)	21 (51%)
Mild	7 (16%)	4 (10%)
Moderate	17 (40%)	15 (37%)
Severe	1 (2%)	1 (2%)
Genetic mutation type		
Truncating mutation	24 (56%)	28 (68%)
In-frame del-dup or missense mutation	18 (42%)	11 (27%)
Microdeletion	1 (2%)	1 (2%)
Unclassified variant	0	1 (2%)
NF1 inheritance		
Familial	22 (51%)	19 (46%)
Sporadic	21 (49%)	20 (49%)
Unknown	0	2 (5%)
Education type		
Regular	20 (46%)	24 (58%)
Special	23 (54%)	17 (42%)
Parental Occupation§		
Lower	18 (42%)	13 (32%)
Middle	13 (30%)	15 (37%)
Higher	12 (28%)	13 (32%)
Total cholesterol, mmol/L	4·17 (0·57)	4·30 (0·75)
LDL cholesterol, mmol/L	2·33 (0·54)	2·41 (0·65)
Dose group in months 3-12		
20 mg/d or placebo	29 (67%)	23 (56%)
40 mg/d or placebo	14 (33)%	18 (44%)

Data are median (IQR), number (%), or mean (SD). WISC-III-NL=Wechsler intelligence scale for children, third edition, Dutch translation. CBCL=parent-reported child behaviour checklist. NF1=neurofibromatosis type 1. LDL=low-density lipoprotein. *Higher is better. †Lower is better. ‡NF1 disease severity was scored according to the Riccardi scale, modified to exclude cognitive aspects of NF1.[6] §Classification of parental occupation was done according to data from the Dutch central bureau of statistics (which uses a five-level scale), which we used to apply our own three-level scale. Doses were decided based on the patient's age.

[95% CI –3·8 to 1·3]; p=0·33), attention problems (–1·6 T-score points [–4·3 to 1·0]; p=0·23), or internalising behavioural problems (–0·1 [–3·3 to 3·1]; p=0·96) when adjusted for baseline performance (table 2). Additional adjustment for age and sex produced similar results (table 2). Simvastatin had no significant effects on any of the secondary outcome measures, including visual-spatial memory and attention (table 2). Figure 2 shows the standardised treatment effects on primary and secondary outcome measures.

After 1 month (10 mg simvastatin per day), mean total cholesterol in the simvastatin group had decreased by 0·78 mmol/L (95% CI 0·54–1·03) more than it had in the placebo group and LDL cholesterol decreased by 0·79 mmol/L (0·56–1·01). Cholesterol concentrations had decreased no further at 6, 9, or 12 months. HDL cholesterol and triglycerides remained stable over the course of the study (appendix). Most adverse events were mild or moderate and frequency was similar between groups (table 3). 38 (88%) of 43 patients in the simvastatin group and 39 (95%) of 41 patients in the placebo group reported at least one adverse event. No increased incidence of myalgia, myopathy, or rhabdomyolysis was reported in patients given simvastatin compared with patients given placebo (appendix). Serious adverse events occurred in six patients: two in the simvastatin group and four in the placebo group. These events included continuing growth of plexiform neurofibromas (in two patients receiving simvastatin and one patient receiving placebo) and progressive scoliosis (two patients receiving placebo), all requiring surgery, and hospital admission for gastritis (one patient receiving placebo).

Table 2. Primary and secondary outcome measures at baseline and 12-month follow-up

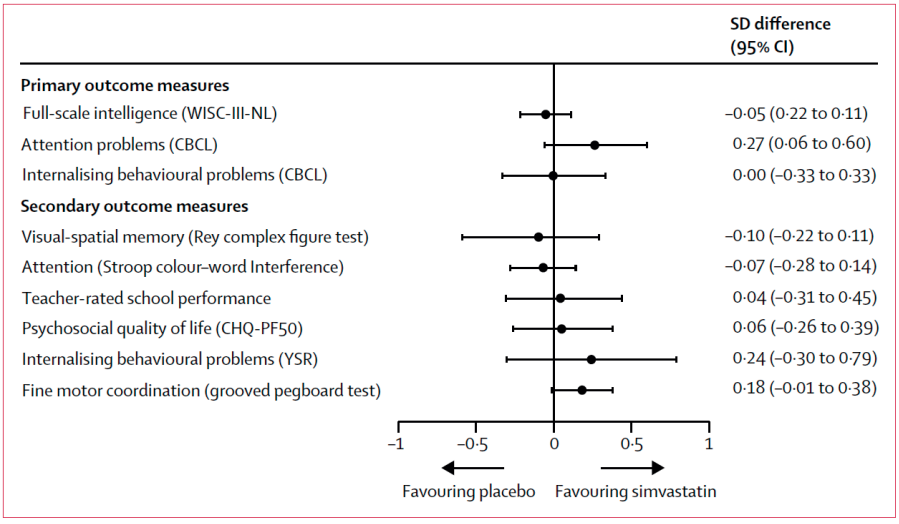
	Simvastatin	Placebo	Adjusted for baseline score		Adjusted for baseline score, age and sex	
			Treatment effect (95% CI)	*p*	Treatment effect (95% CI)	*p*
Primary outcome measures						
Full-scale intelligence (WISCIII-NL)*	n = 43	n = 39	-1·3 (-3·8 – 1·3)	0·33	-0·8 (-3·4 – 1·8)	0·56
Baseline IQ	83·8 (16·1)	82·3 (15·5)	"	"	"	"
12 months IQ	85·7 (18·0)	85·4 (16·4)	"	"	"	"
Attention problems (CBCL)†	n = 42‡	n = 39	-1·6 (-4·3 – 1·0)	0·23	-2·2 (-5·0 – 0·5)	0·11
Baseline *T*-score	61·1 (9·0)	62·0 (7·6)	"	"	"	"
12 months *T*-score	58·8 (7·4)	60·9 (9·0)	"	"	"	"
Internalizing behavioural problems (CBCL)†	n = 42‡	n = 39	-0·1 (-3·3 – 3·1)	0·96	0·0 (-3·4 – 3·4)	0·99
Baseline *T*-score	54·9 (10·6)	56·1 (10·0)	"	"	"	"
12 months *T*-score	54·0 (9·0)	54·9 (10·0)	"	"	"	"
Secondary outcome measures						
Visual-spatial memory (Rey Complex Figure test – delayed recall)*	n = 42§	n = 39	-0·2 (-0·6 – 0·2)	0·34	-0·1 (-0·6 – 0·3)	0·50
Baseline *Z* score	-2·0 (0·9)	-2·0 (1·1)	"	"	"	"
12 months *Z* score	-1·9 (1·0)	-1·7 (1·2)	"	"	"	"
Attention (Stroop Colour Word Interference)†	n = 41¶	n = 37¶	7·5 (-1·3 – 16·2)	0·14	2·8 (-5·9 – 11·7)	0·55
Baseline raw score	72 (39)	64 (45)	"	"	"	"
12 months raw score	59 (31)	47 (27)	"	"	"	"

Teacher rated school performance*	n = 34||	n = 30||	0·2 (-0·6 – 0·9)	0·64	0·1 (-0·7 – 1·0)	0·74
Baseline raw score	5·8 (2·2)	5·7 (2·4)	"	"	"	"
12 months raw score	6·2 (1·9)	6·0 (1·9)	"	"	"	"
Psychosocial Quality of Life (CHQ-PF50)*	n = 40**	n = 38**	0·02 (-0·22 – 0·25)	0·89	0·04 (-0·20 – 0·29)	0·72
Baseline	-0·06 (0·80)	-0·07 (0·74)	"	"	"	"
12 months	0·15 (0·69)	0·13 (0·80)	"	"	"	"
Internalizing behavioural problems (youth self-report)†	n = 23††	n = 24††	-1·7 (-6·5 – 3·1)	0·48	-2·5 (-8·1 – 3·1)	0·37
Baseline *T*-score	56·4 (11·9)	53·0 (8·3)	"	"	"	"
12 months *T*-score	51·9 (9·9)	51·7 (9·8)	"	"	"	"
Fine motor coordination (grooved pegboard test, dominant hand)†	n = 43	n = 39	-3·8 (-8·8 – 1·3)	0·14	-4·9 (-10·2 – 0·3)	0·07
Baseline	94 (29)	84 (23)	"	"	"	"
12 months	80 (18)	79 (18)	"	"	"	"

Data are mean (SD), unless otherwise specified. WISC-III-NL=Wechsler intelligence scale for children, third edition, Dutch translation. CBCL=parent-reported child behaviour checklist. CHQ-PF50=child health questionnaire–parent form 50. *Higher is better. †Lower is better. ‡Data missing for one patient in the simvastatin group because the questionnaire was not returned by the parents. §Data missing for one patient in the simvastatin group because they were omitted from the test battery erroneously. ¶Data missing for two patients in each group because they were unable to take the test because of reading disability. ||Data missing for nine patients in each group because arithmetic and language topics were classified by teachers as not applicable to these patients. **Data missing for one patient in the simvastatin group because the questionnaire was not returned, and for two patients in the simvastatin group and one in the placebo group because essential items were not completed on the checklist. ††Children younger than 11 years were deemed too young to be given the youth self-report form (20 patients in the simvastatin group; 15 patients in the placebo group).

Results of laboratory screens showed a few mild and transient increases in liver enzymes and creatine kinase in both groups (table 3); none led to cessation of treatment. No participants reached the predefined lower limits for total cholesterol, HDL-cholesterol, or triglycerides (non-fasting). In the simvastatin group, seven children had one (n=3) or more (n=4) LDL cholesterol measurements below the predefined lower threshold, but no action was recommended by the data and safety monitoring board, since other values were within the normal range. Nine (53%) of 17 girls receiving simvastatin advanced one or more Tanner stages of puberty during the trial, compared with 16 (67%) of 24 receiving placebo. 14 (54%) of 26 boys receiving simvastatin and seven (54%) of 13 receiving placebo advanced one or more Tanner stages. Two girls in the placebo group were not included in this analysis because they did not undergo post-baseline Tanner stage assessments.

Figure 2: Standardised treatment effects.



The effect of simvastatin on primary and secondary outcome measures, adjusted for baseline performance, age, and sex. Treatment effects have been converted to SD difference and are accompanied by the corresponding 95% CI. WISC-III-NL = Wechsler intelligence scale for children, third edition, Dutch translation. CBCL = parent reported child behaviour checklist. CHQ-PF50 = child health questionnaire–parent form 50. YSR = youth self-report.

Discussion

Here we present the outcome of our randomised, double-masked, placebo-controlled trial aimed at improving cognitive deficits in children with neurofibromatosis type 1. Our results showed that simvastatin treatment for 12 months had no effect on full-scale intelligence, attention problems, or internalising behavioural problems. Moreover, we found no indications of efficacy on a carefully selected range of predefined secondary outcome measures. Hence, this trial refutes a role for simvastatin in treatment of cognitive or behavioural problems in children with neurofibromatosis type 1. Unfortunately, despite the many promising drugs that have been identified in mouse models of cognitive disorders, translational studies with placebo-controlled trial designs are rare for cognitive disorders caused by single-gene mutations. This situation is also true for neurofibromatosis type 1 (panel). The absence of good clinical studies encourages off -label prescription, which is a major concern, particularly when the drug is readily available to the patient. In this study, the cognitive and behavioural profile of the study population at baseline (table 1) was fairly representative of the cognitive profile in the general neurofibromatosis type 1 population.[3–5,8] Sample size was adequate, because we could confidently rule out a positive change of more than 1.3 points in full-scale intelligence, a reduction of attention problems of more than 4·3 T-score points, and a reduction of internalising behavioural problems of more than 3·3 T-score points (table 2). Furthermore, we achieved a low attrition rate and high medication compliance, which suggests that medium-term to long-term trials for cognitive dysfunction are feasible in this population. The dosing was based on the maximum recommended daily dose for treatment of children with familial hypercholesterolaemia.[19] At least in the liver, maximal inhibition of the HMG-CoA reductase pathway was achieved in patients on simvastatin, shown by the substantial reduction of blood cholesterol concentrations after 1 month (appendix). Whether similar inhibition of the HMG-CoA reductase pathway was achieved in the brain is unknown. It is possible that higher doses are necessary to achieve biological effects in human beings. However, increasing the dose would increase safety concerns, including the risk of myopathy, which was 30 times higher (0·9%) in adults on 80 mg per day of simvastatin than in those on 20 mg per day.[23] Although 12 months of simvastatin was not related to any adverse events, this study was not powered to detect rare effects.

Table 3: Adverse events

	Simvastatin (n=43)		Placebo (n=41)	
	Grade 1-2	**Grade 3**	**Grade 1-2**	**Grade 3**
Adverse events by system organ class				
Gastrointestinal system disorders	23 (17)	0	25 (21)	1 (1)
General, whole-body disorders	16 (16)	0	25 (20)	0
Skin and appendage disorders	12 (10)	0	11 (10)	0
Musculoskeletal system disorders	8 (7)	0	13 (11)	0
Respiratory system disorders	12 (11)	0	5 (5)	0
Central and peripheral nervous system disorders	9 (8)	0	6 (6)	0
Neoplasms (eg, aggravated neurofibroma)	2 (2)	2 (2)	3 (2)	1 (1)
Psychiatric disorders	2 (2)	0	4 (4)	0
Urinary system disorders	2 (2)	0	4 (4)	0
Secondary events (eg, postoperative pain)	3 (3)	0	1 (1)	2 (2)
Resistance mechanism disorders	4 (4)	0	2 (2)	0
Vision disorders	1 (1)	0	3 (3)	0
Other systems	1 (1)	0	3 (3)	0
Laboratory Adverse Events				
Raised alanine transaminase	6 (6)	0	1 (1)	0
Raised aspartate transaminase	3 (3)	0	5 (5)	0
Raised creatine kinase (CK)	1 (1)	0	1 (1)	0

Data are number of events (number of patients who had an event). Adverse events are grouped by system organ class according to WHO adverse reaction terminology. A complete list of adverse events is presented in the appendix.

Of note, a lower proportion of girls receiving simvastatin advanced one or more pubertal stages than did those receiving placebo, which was non-significant and might simply be attributed to age differences between the groups. Nonetheless, future studies of statin treatment in other populations of normocholesterolaemic children and adolescents should monitor puberty development.

We assumed 12 months of treatment was long enough to measure effects on full-scale intelligence. In support of this view, results of 1 year randomised studies showed that full-scale intelligence can improve in children with attention deficit hyperactivity disorder who receive stimulant medication[24] and in healthy children taking music lessons.[25] However, how much time a

model and patients.[11,12,31] Nevertheless, in view of the results of our trial, further insight into the pathophysiology of neurofibromatosis type 1 will be necessary to explore other targetable disease mechanisms.

Panel: Research in context

Systematic review

We did a systematic search of PubMed on July 8, 2013, for additional cognitive trials in neurofibromatosis type 1. Search terms included "neurofibromatosis", "cognition", "attention", "behaviour", and "clinical trial". Of 25 articles found, four described three clinical trials in patients with neurofibromatosis type 1. A 12 week randomised placebo-controlled trial in 61 children with neurofibromatosis type 1 showed no effect of simvastatin on cognitive function and MRI abnormalities, with the notable exception of the significant effect on one secondary outcome measure: the object assembly subtask of the Wechsler intelligence scale for children.[6] Furthermore, results of a phase 1 single-arm open-label study of lovastatin in 23 children with neurofibromatosis type 1 suggested lovastatin improved memory and attention, accompanied by normalisation of default network functional connectivity measured with resting-state functional MRI in a subset of the participants.[15,16] These seemingly encouraging results might be attributable to normal cognitive development, test–retest improvements, or placebo effects. A third study was a single-arm 1 year study of methylphenidate to treat attention problems in children with neurofibromatosis type 1 and comorbid attention deficit hyperactivity disorder, and results showed a decrease in attention problems in children who received the drug.[22]

Interpretation

In this 12 month trial, use of simvastatin provided no benefit over placebo on full-scale intelligence, behavioural problems, visual-spatial memory, attention, motor coordination, school performance, and quality of life. These findings are in contrast with results from the previous single-arm study,[15,16] but largely consistent with the smaller randomised controlled trial that measured short-term effects of simvastatin on neuropsychological test scores and MRI abnormalities.[6] We conclude that the number of trials is limited, and more studies are needed to identify effective treatments for cognitive and behavioural problems in children with neurofibromatosis type 1.

Supplementary methods (published Online)

Participants, treatment and follow-up

Patients were eligible for randomization when they were 8·0 to 16·0 years of age and had a genetic confirmation of NF1. Genetic counseling and testing for NF1 is offered routinely at our centers, minimizing selection. Informed oral and written consent was obtained from parents or guardians and oral and written informed assent was obtained from participants aged 12 years and older. Exclusion criteria were use of neurotropic medication or current simvastatin use; symptomatic central nervous system abnormalities; insufficient comprehension of the Dutch language; severely impaired vision or deafness; segmental NF1 and IQ below 48, which is the detection limit for Wechsler Intelligence Scales for Children.

Study design and setting

We performed an investigator-initiated randomized, parallel group, double-masked, placebo-controlled, one-year clinical trial in children with NF1 between March 9, 2010 and March 5, 2013. This was a two-center study at Erasmus University Medical Center, Rotterdam, the Netherlands, and University Hospital Leuven, Belgium, both national referral centers for Neurofibromatosis type 1. Approval was obtained from the Central Committee on Research involving Human Subjects (The Hague, The Netherlands) and the Ethical Committee of University Hospital Leuven (Belgium) and performed in agreement with Declaration of Helsinki (2008 version) and Good Clinical Practice guidelines. Full source data verification was performed and all data queries had been solved before unmasking. All authors subscribe to adherence to the study protocol.

Intervention

Participants were treated with simvastatin or identical placebo once daily in the morning. The doses were carefully selected at the maximal daily dose recommended for children with familial hypercholesteremia: 10 mg/d in the first month, 20 mg/d in the second month, and fixed at 20 mg/d for children aged ≤ 12 years or 40 mg/d for adolescents aged 13·0 years and older in months 3 – 12. Treatment group assignments were masked for participants, investigators, and outcome assessors. Simvastatin and placebo capsules were produced by the hospital pharmacy. Capsules were identical in color, shape, size, weight, smell, and taste. The simvastatin capsules contain the active substance, simvastatin (Spruyt hillen bv, IJsselstein, The Netherlands), and as excipients siliciumdioxide colloidal (as glidant), magnesium stearate (as lubricant, diluent), cellulose microcrystalline (as binder, diluent) and lactose (as volume filler). The placebo capsules contain all of the abovementioned components, except the active substance. They were dispensed by the

hospital pharmacy in containers consisting of 35 capsules per month, allowing some flexibility in the planning of follow-up visits. Left-over capsules had to be returned and counted for compliance. To avoid unmasking of investigators during the trial, the independent Data and Safety Monitoring Board (Drs. Hop, de Rijke, de Klerk, de Heus, Erasmus MC) reviewed cholesterol levels during the study and primary analysis phase. Randomization was generated by the department of Biostatistics at Erasmus MC (dr. Hop) and implemented by the local hospital pharmacist (Erasmus MC: dr. Zaal; UH Leuven: dr. de Gieter) using computer generated, permuted block randomization lists, using blocks of 10 participants stratified by center. Patients were assigned a medication number in the order of their enrollment. Treatment allocation was concealed from all participants and investigators.

Sample size calculation indicated that inclusion of 84 participants had a power of 85% with an alpha of 0.05 of detecting a clinically relevant effect of 7.5 IQ-points (equivalent to 0.5 standard deviation) difference between simvastatin and placebo on the primary outcome measure. The before-after design of the trial allows for the incorporation of test-retest correlation. No data was available on the one-year test-retest correlation of the WISC-III-NL, but 2-year correlation is 0.91[s1]. We estimated correlation after one-year at a conservative 0.69.

Outcome measures

Outcome measures were assessed at baseline and after 12 months of treatment. All neuropsychological tests were developed for children and were administered in their Dutch versions. For most outcome measures, age standardized scores were used. Population average for IQ is 100 and the standard deviation is 15, with higher scores indicating better performance. For CBCL, and YSR, data were represented as T-scores, with a population average of 50 and standard deviation of 10, with a higher score indicating more problems. Teacher reported school performance was calculated on a scale from 2 to 10, by summation of five-point scores on topics of Language and Arithmetic. Higher scores indicate better performance. Health-related Quality of life (CHQ-PF50) and Rey complex figure test are presented using z-scores, with 0 indicating the mean for the norm sample with a standard deviation of 1. For teacher reported school performance, Stroop Color Word test and grooved pegboard test, raw scores are used, since no appropriate norm groups are available for the entire age-range. Before and after measurements were performed by the same neuropsychologist AR or EP. Any age or gender confounding effects in the estimation of treatment effects are accounted for by multivariable analysis. Harms were monitored during monthly contacts with the investigators. Outpatient visits were scheduled at baseline and after 1, 3, 6, 9 and 12 months. In the intervening months, harms and study

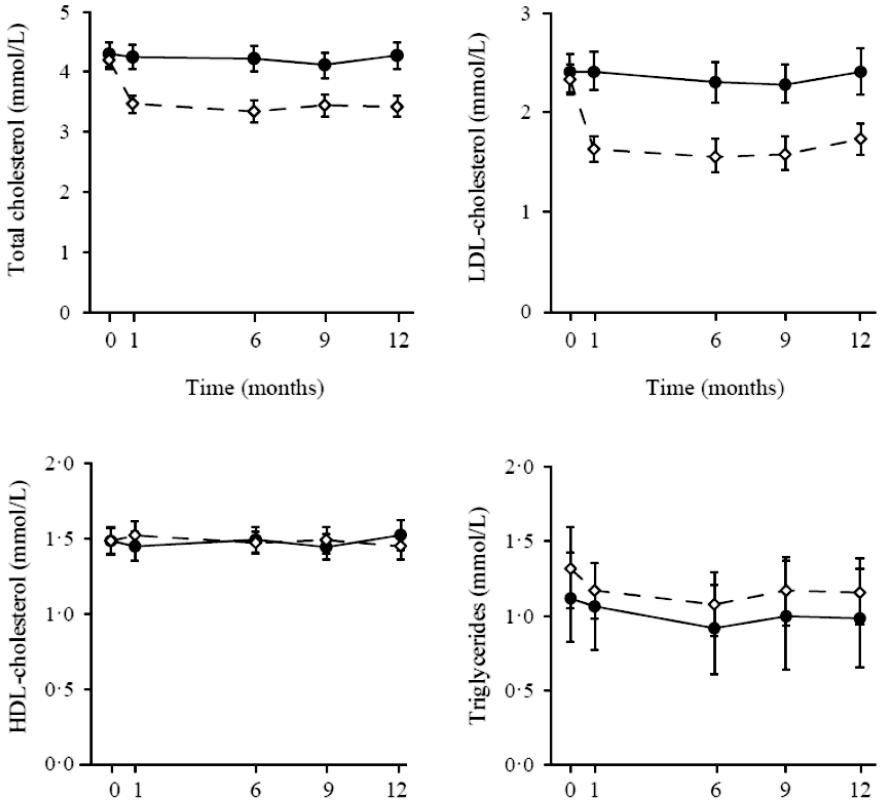
compliance were monitored by telephone interviews. Participants were provided with a diary in which they were instructed to note any deviations from treatment protocol and possible adverse events. At each consult, one of the study physicians recorded any adverse events and serious adverse events (adverse events that were life-threatening, causing disability, or requiring hospitalization) with a standardized checklist containing simvastatin associated sideeffects, supported by open questions and a review of the participant's diary. Standard internal and neurological clinical exams were performed and blood was drawn by phlebotomy for laboratory examination at visits after 1, 6, 9 and 12 months of treatment. Hypothetically, cholesterol reduction could influence sex hormone production. Therefore, Tanner stages for puberty development were noted. Laboratory screening parameters were measured according to standard hospital laboratory protocol; alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine phosphokinase (CK) to screen for laboratory adverse events; total cholesterol (tChol), highdensity lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides to assess lower limits of lipid levels and to monitor compliance. Criteria for discontinuation of study medication were a persistent increase of more than 3-fold the upper limit of normal (ULN) ALT or AST levels, more than 10- fold the ULN for CK levels with or without muscular symptoms, or 5- to 10-fold the ULN for CK levels with muscular symptoms. Lower limits of cholesterol in blood in children do not exist, but children would stop study medication if these levels decreased with 3x standard deviation of the population norms, as assessed by the independent Data and Safety Monitoring Board to avoid premature unmasking. Adverse events were categorized according to WHO-ART nomenclature[s2], and tabulated. No significance testing has been performed on adverse events, since statistical power to detect significant differences is low. All adverse events are therefore displayed using counts. For puberty development, Tanner stage change was defined as any change during the study versus no change during the study. Logistic regression analysis was performed by adjusting for lowest baseline Tanner scale. Adjusting for lowest baseline scale, age and sex were used to reveal significant changes. Lipid blood levels were analyzed over the course of the trial using the generalized linear mixed model procedure with time x treatment as the variable of interest. The statistical analysis plan and any exclusion from the intention to treat set were finalized before unmasking. All reported adverse events were scored as being not drug related, possibly drug related, or definitely drug related prior to unmasking.

Statistical analysis

No statistical testing was performed for baseline study group differences. Intention to treat analysis was performed for all participants of whom post-baseline data was available, without imputation of missing values. Primary and secondary outcome measures were analyzed using bivariable linear regression for the effect of treatment group on the score at 12-month visit, adjusting for baseline performance. Multivariable regression was performed by adjusting treatment effects for baseline performance, age and sex. We planned to determine effect modification of outcome parameters using interaction term of treatment and age and baseline, only if main effects were present. If interaction terms treatment x baseline score would have shown significant effect modification, subgroup analysis was planned for groups with -1SD lower scores at baseline. The analysis plan was determined before unmasking and compiled according to the study protocol. All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. All authors had full access to all trial data and assume final responsibility for the decision to submit the manuscript for publication.

Role of funding sources

Non-commercial funding was provided by The Netherlands Organization for Health Research and Development (ZonMw), the Marguerite-Marie Delacroix Foundation and Research Foundation Flanders (FWO-Vlaanderen) and the Dutch Neurofibromatosis Association (NFVN). The funding sources had no role in the conception, design and analysis of the trial, the writing of the manuscript or the decision to publish the results.



Online supplementary figure 1: Estimated means for total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Black circles = placebo. White diamonds = Simvastatin. Error bars represent 95% confidence intervals.

Acknowledgments

We thank all children and families for participating in this trial. We thank B Manai, A de Goede-Bolder, C P Bouman, R Zaal, and S Vandenput for assistance during study conduct and E W Steyerberg, J B C de Klerk, Y B de Rijke, L C Krab, and S A Kushner for valuable discussions. We also thank clinicians throughout the Netherlands and Belgium for referring patients, and the Dutch and Flemish patient organisations (Neurofibromatose Vereniging Nederland, NF-Kontakt) for their ongoing support.

References

1 Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010; 152A: 327–32.

2 Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007; 44: 81–88.

3 Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005; 65: 1037–44.

4 Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008; 23: 1002–10.

5 Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. Child Neuropsychol 2011; 17: 313–29.

6 Krab LC, de Goede-Bolder A, Aarsen FK, et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008; 300: 287–94.

7 Garg S, Lehtonen A, Huson SM, et al. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. Dev Med Child Neurol 2013; 55: 139–45.

8 Hyman SL, Arthur Shores E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Dev Med Child Neurol 2006; 48: 973–77.

9 Krab LC, Oostenbrink R, de Goede-Bolder A, Aarsen FK, Elgersma Y, Moll HA. Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior. J Pediatr 2009; 154: 420–25.

10 Descheemaeker MJ, Plasschaert E, Frijns JP, Legius E. Neuropsychological profile in adults with neurofibromatosis type 1 compared to a control group. J Intellect Disabil Res 2013; 57: 874–86.

11 Costa RM, Federov NB, Kogan JH, et al. Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. Nature 2002; 415: 526–30.

12 Cui Y, Costa RM, Murphy GG, et al. Neurofibromin regulation of ERK signaling modulates GABA release and learning. Cell 2008; 135: 549–60.

13 Shilyansky C, Karlsgodt KH, Cummings DM, et al. Neurofibromin regulates corticostriatal inhibitory networks during working memory performance. Proc Natl Acad Sci USA 2010; 107: 13141–46.

14 Li W, Cui Y, Kushner SA, et al. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. Curr Biol 2005; 15: 1961–67.

15 Acosta MT, Kardel PG, Walsh KS, Rosenbaum KN, Gioia GA, Packer RJ. Lovastatin as treatment for neurocognitive deficits in neurofibromatosis type 1: phase I study. Pediatr Neurol 2011; 45: 241–45.

16 Chabernaud C, Mennes M, Kardel PG, et al. Lovastatin regulates brain spontaneous low-frequency brain activity in neurofibromatosis type 1. Neurosci Lett 2012; 515: 28–33.

17 Chong PH, Seeger JD, Franklin C. Clinically relevant differences between the statins: implications for therapeutic selection. Am J Med 2001; 111: 390–400.

18 Sierra S, Ramos MC, Molina P, Esteo C, Vazquez JA, Burgos JS. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J Alzheimers Dis 2011; 23: 307–18.

19 de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation 2002; 106: 2231–37.

20 Brems H, Chmara M, Sahbatou M, et al. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet 2007; 39: 1120–26.

21 Verhulst FC, Van der Ende J, Koot HM. Handleiding voor de CBCL/4–18. Rotterdam: Academic Medical Center Rotterdam/Erasmus University, Sophia Children's Hospital, Department of Child and Adolescent Psychiatry, 1996.

22 Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Dev Med Child Neurol 2002; 44: 164–70.

23 Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010; 376: 1658–69.

24 Gillberg C, Melander H, von Knorring AL, et al. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial. Arch Gen Psychiatry 1997; 54: 857–64.

25 Schellenberg EG. Music lessons enhance IQ. Psychol Sci 2004; 15: 511–14.

26 ClinicalTrials.gov. A randomized placebo-controlled study of lovastatin in children with neurofibromatosis type 1 (STARS). http://clinicaltrials.gov/show/NCT00853580 (accessed Aug 5, 2013).

27 van Engelen SJ, Krab LC, Moll HA, et al. Quantitative differentiation between healthy and disordered brain matter in patients with neurofibromatosis type I using diffusion tensor imaging. AJNR Am J Neuroradiol 2008; 29: 816–22.

28 Pride N, Payne JM, Webster R, Shores EA, Rae C, North KN. Corpus callosum morphology and its relationship to cognitive function in neurofibromatosis type 1. J Child Neurol 2010; 25: 834–41.

29 Silva AJ, Frankland PW, Marowitz Z, et al. A mouse model for the learning and memory deficits associated with neurofibromatosis type I. Nat Genet 1997; 15: 281–84.

30 Ullrich NJ, Ayr L, Leaff er E, Irons MB, Rey-Casserly C. Pilot study of a novel computerized task to assess spatial learning in children and adolescents with neurofibromatosis type 1. J Child Neurol 2010; 25: 1195–202.

31 Violante IR, Ribeiro MJ, Edden RA, et al. GABA deficit in the visual cortex of patients with neurofibromatosis type 1: genotype-phenotype correlations and functional impact. Brain 2013; 136: 918–25.

Online supplementary references

s1. Kort W, Schittekatte M., Dekker, P.H., Verhaeghe, P., Compaan, E.L., Bosmans, M., Vermeir, G. WISC-III NL Wechsler Intelligence Scale for Children. Derde Editie NL. Handleiding en Verantwoording. Amsterdam: Hartcourt Test Publishers/Nederlands Instituut voor Psychologen; 2005.

s2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255-9.

CHAPTER 7.

Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1

van der Vaart T, Rietman AB, Plasschaert E, Legius E, Elgersma Y, Moll HA, NF1-SIMCODA Study Group

Neurology 2016;86:154-160

Abstract

Objective: Clinical trials for behavioral problems and cognitive deficits in Neurofibromatosis type 1 (NF1) are emerging. This study aims to evaluate the appropriateness of outcome measures by analyzing the degree of deficits compared to reference groups, test-retest reliability, and how scores correlate between outcome measures.

Methods: Data were analyzed from NF1-SIMCODA, a randomized placebo-controlled trial of simvastatin for cognitive deficits and behavioral problems in children with NF1. Outcome measures were compared with age-specific reference groups to identify domains of dysfunction. Pearson's r was computed for before-and-after-measurements within the placebo group to assess test-retest reliability. Principal component analysis was used to identify the internal structure in the outcome data.

Results: Strongest mean score deviations from the reference groups were observed for full-scale intelligence (-1.1 SD), Rey-complex-figure-test (RCFT) delayed-recall (-2.0 SD), Attention problems (-1.2 SD) and Social problems (-1.1 SD). Long-term test-retest reliability were excellent for Wechsler-scales ($r > 0.88$), but poor-to-moderate for other neuropsychological tests (r range: 0.52 – 0.81) and Child-Behavioral-Checklist (CBCL) subscales (r range: 0.40 – 0.79). The correlation structure revealed two strong components in the outcome measures, "Behavior" and "Cognition", with no correlation between these components. Scores on psychosocial-quality-of-life correlate strongly with behavioral problems and less with cognitive deficits.

Conclusions: Children with NF1 show distinct deficits in multiple domains. Many outcome measures showed weak test-retest correlations over the one-year trial period. Cognitive and behavioral outcomes are not interchangeable. This analysis demonstrates the need to include reliable outcome measures on a variety of cognitive and behavioral domains in clinical trials for NF1.

Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder with a birth-incidence of 1:2,700, caused by mutations or deletions in the NF1 gene.[1, 2] Clinical diagnostic criteria include multiple café-au-lait spots, skinfold freckling, various types of neurofibroma, NF1-specific bony dysplasia, optic pathway glioma and Lisch noduli of the iris.[3] Learning disabilities, cognitive deficits and behavioral problems in various domains are reported in up to 80% of children with NF1, but similar to the somatic complications of NF1 cognitive and behavioral problems are highly variable. Full-scale intelligence is 10-15 IQ-points lower than in the population and in sibling controls. Thirty-three to fifty percent of children with NF1 fulfill criteria for Attention-deficit-hyperactivity disorder (ADHD)[4-6] and Internalizing behavioral are frequently observed.[6] Specific deficits in visuospatial memory and motor coordination are prevalent.[6, 7]

Several promising therapeutic options are emerging from preclinical studies of the cognitive and behavioral deficits in NF1. Neurofibromin, the protein product of the NF1 gene, has a GTP-ase activating (GAP) domain which is involved in the regulation of p21-RAS, a proto-oncogene implicated in tumor formation.[8, 9] Increased RAS-signaling in inhibitory interneurons has a major role in the learning deficits in Nf1 mice. [10-12] Lovastatin, a cholesterol-lowering agent, improved learning deficits of Nf1 mice, potentially through RAS-inhibition.[13] Other candidate drugs are L-dopamine and methylphenidate, both shown to be effective on attention problems in an Nf1 mouse model in which neurofibromin was selectively knocked-out in neuroglial-progenitor cells.[14, 15] Another recent study found Lamotrigine to be effective in treating cognitive deficits in two separate Nf1 mouse models, through regulation of the excitability of inhibitory interneurons.[16]

Six clinical trials aimed at treating cognitive deficits in NF1 are reported in literature, varying in design, size, treatment and treatment duration. Outcome measures that were used varied widely (table 1). Reasons for this lack of consensus may include the variability of the neuropsychological spectrum in NF1, the divergence of theories regarding the pathophysiology, the desire to select tests paralleling the mouse findings, and the absence of clear positive effects in preceding trials. The NF1-SIMCODA randomized controlled trial

Table 1. Cognitive clinical trials in Neurofibromatosis type 1 and their outcome measures

Reference	Drug & Design	*n*	Age (years)	Inclusion criteria	Treatment duration	Outcome measures	Conclusions
Mautner et al., 2003 [37]	Methylphenidate Single arm	20	Mean: 10.7, *SD* 2.2	Diagnosis of ADHD	12 months	TOVA CBCL	Methylphenidate improves attention in children with NF1 and ADHD
Krab et al., 2008 [18]	Simvastatin Randomized parallel-group placebo-controlled	61	Range: 8-16	No selection	12 weeks	Rey CFT; Cancellation test; Prism adaptation; MRI ADC-values; Stroop CWT; Block design; Object assembly; JLO	Simvastatin similar to placebo on all outcomes, except for improvement on object assembly
Acosta et al., 2011 [38]	Lovastatin Single arm	23	Range: 10-17	IQ >80; history of learning disabilities	12 weeks	TEA-Ch CVLT WRAML-2	Improvements in areas of verbal and nonverbal memory after lovastatin use
Mainberger et al., 2013 [39]	Lovastatin (high dose) Cross-over placebo-controlled	10	Range: 19-44	No psychotropic medications	4 days	TAP TMS-PAS/SICI	Increased phasic alertness and synaptic plasticity, and decrease of intracortical inhibition
Van der Vaart et al., 2013 [17]	Simvastatin Randomized parallel-group placebo-controlled	84	Range: 8-16	No stimulant medication	12 months	*See introduction and table 2*	Simvastatin similar to placebo
Lion-Francois et al., 2014[40]	Methylphenidate, cross-over placebo-controlled	39	Range: 7-13	IQ between 80 -120; anamnestic attention problems or school problems	4 weeks	sCPRS; CTRS; CDRs-R; CDI; STAIc	Methylphenidate improves attention in children with NF1 and ADHD

NF1: Neurofibromatosis type 1; ADHD: Attention deficit/hyperactivity disorder; TOVA: Test of Variables of Attention; CBCL: Child Behavioral Checklist; Rey CFT: Rey complex figure test; MRI ADC: magnetic resonance imaging apparent diffusion coefficient; Stroop CWT: Stroop colour word interference test; JLO: judgement of line orientation; TEA-Ch: Test of Every-Day Attention for Children; CVLT: California Verbal Learning Test for Children; WRAML-2: Wide Range Assessment of Memory and Learning, Second Edition; TAP: Test of Attentional Performance; TMS: transcranial magnetic stimulation; PAS: paired associative stimulation; SICI: short interval cortical inhibition; sCPRS: simplified Conners' Parent Rating Scale; CTRS: Conners' Teacher Rating Scale; CDRs-R: Children's Depression Rating Scale; CDI: Children's Depression Inventory; STAIc: State-trait Anxiety Inventory for Children

(acronym for "Simvastatin on Cognition and Daily life") evaluated the effects of 12-month simvastatin treatment on cognitive functioning and behavioral problems in children with NF1 aged 8 – 16 years. Simvastatin did not have any positive effect on cognitive functioning, behavioral problems or school performance.[17] The outcome measures for NF1-SIMCODA were carefully selected based on earlier experience from our earlier trial with shorter (three-month) duration[18] and the notion that longer study duration of 12 months allows for better detection of changes in global cognitive functioning, everyday behavioral problems, and school performance. Therefore, the primary outcome measures in NF1-SIMCODA were full-scale intelligence measured with the Wechsler Intelligence Scales for Children-III (WISC-III), and the Attention Problems scale and the Internalizing Behavioral Problems scales of a parent-rated questionnaire, the CBCL.[17] The relevance of the CBCL is demonstrated by its correlation with psychosocial quality of life in children with NF1.[19] Regarding secondary outcomes, we included more specific neuropsychological tests: the RCFT, the Stroop Color Word interference task (Stroop CWT) and the Grooved pegboard test. Other secondary outcome measures were teacher-rated school performance, psychosocial quality of life by Child-Health questionnaire (CHQ), and self-reported Internalizing behavioral problems.

This paper analyzes the scores on outcome measures used in the NF1-SIMCODA study. We investigated three main questions. 1) Which outcome measures were most affected in comparison to normative reference groups? Although previous studies have resulted in a set of tests that are reliably affected by NF1,6 uncertainty remains about the performance on these tasks in a clinical trial population. Tests on which children with NF1 score within the normal range are less suitable as outcome measure in a trial. 2) What is the one-year test-retest reliability of scores on the outcome measures used? Trials designed with before – after measurements using reliable tests reduce the number of subjects needed and increases power.[20] 3) How are the scores on the various outcome measures correlated? Scores for cognitive outcome measures and behavioral problems are correlated in the general population, where lower intelligence is correlated with increased incidence of emotional, behavioral, and social problems.[21] It is unclear whether this is also true within the NF1 population. In addition, what outcome measures are correlated to health-related quality of life? The questions above are important when selecting appropriate outcome measures in trials involving patients with NF1.

Method

Patient population

The data from 84 children who participated in NF1-SIMCODA trial were analyzed.[17] The trial is registered with the Netherlands Trial Registry (www.trialregister.nl, NTR2150). The children had a median age of 11.5 years (range: 7.9 – 16.0), with 45 of them female (54%). Informed consent was obtained and local and national institutional review boards approved the protocol.

Outcome measurements

In addition to the pre-specified outcome measures (see introduction),[17] we have added the following outcome measures to the current analysis: 1) cognition data, a distinction between verbal and performance intelligence on the WISC-III-NL; RCFT copy, although delayed recall is more heavily affected in children with NF1, scores for the direct copy might show already large effects, contributing to the deficit on the delayed recall; 2) behavioral data from questionnaires from parent, youth self-report and teacher questionnaires on total problems, attention problems, social problems, and internalizing emotional and behavioral problems (e.g. anxiety or depression-like behavior).

Data analysis

Baseline scores were used from all included participants (n=84). To allow comparisons of the magnitude of baseline deficits between different scoring systems, outcomes with a standardized scoring system (e.g. IQ-score, Z-scores, or T-scores) were converted into standard deviation scores (SDS) by dividing the effect by the standard deviation in the reference group, such that 0 equals reference group average with a standard deviation of 1. Normality was checked using Shapiro-Wilk tests, and visual inspection of histograms. If any of these violated assumptions of normality, nonparametric tests were used. Differences between the NF1 group and the reference group were tested using independent t-tests for normally distributed data and one-sample Wilcoxon-Signed-Rank tests for non-normally distributed data. Within the placebo group, paired sample t-tests were used to calculate significant before-after differences in normally-distributed data and Wilcoxon-Signed Rank tests for non-normally-distributed data. Differences were considered significant when $p < 0.05$. Data are presented as mean +/- SD, unless otherwise indicated. Pearson product moment correlation analyses were used to examine associations between first and second measurements in the placebo group, as an indication of test-retest reliability and/or

stability. Bivariate normality (linearity) was assessed by inspecting scatter plots.[22] In this exploratory analysis, we did not correct the significance level for multiple testing, given the high a priori probabilities of multiple significant findings in this study and the interdependency of cognitive measures. Methods to control for multiple testing would unreasonably increase the risk of type II error.

Principal component analysis

Since it is likely that scores on certain outcome measures are differentially correlated to other outcome measures, we performed a principal component analysis (PCA). This way, the correlation between outcome measures can be grouped in components and the internal structure of the outcome data can be revealed. We performed PCA for those outcome measures that had complete cases in more than 75% of the sample. We excluded variables from the PCA for which Kaiser-Meyer-Olkin (KMO) measures were low: Stroop CWT (KMO=.50) and Grooved Pegboard test (KMO=.42). The final PCA therefore included outcome measures for behavioral problems (Internalizing behavioral problems, Attention problems, Social problems), cognitive functioning (total performance IQ, verbal IQ, RCFT delayed recall), and health related quality of life (psychosocial quality of life summary scale from CHQ). Principal component analysis was conducted on these seven selected outcome measures with oblique rotation (direct oblimin rotation). The KMO verified the sampling adequacy for the analysis, KMO = .73, and all KMO values for individual items were at least .59 (well above the acceptable limit of .5). An initial analysis was run to obtain eigenvalues for each component in the data. Two components had eigenvalues over Kaiser's criterion of 1 and in combination explained 68% of the variance. The scree plot showed an inflexion that would justify retaining three components. Because this third component had an eigenvalue below .7 (Jollefei's criterion) and the sample size is rather small, we retained two components.

Results

Children with NF1 (8-16 years) had a mean full-scale intelligence (WISC-III) of 83.3 IQ-points (SD 15.6), which is 1.1 SD below population mean (table 1). The largest deviations from the reference group in the cognitive domain were seen on performance IQ (1.1 SD, or 16 IQ-points below population mean) and the RCFT delayed recall (2.0 SD below population mean). Stroop CWT,

Grooved Pegboard test and teacher ratings have incomplete or no Dutch reference groups, therefore the raw scores are displayed. Behavioral problems, as measured by the CBCL, were most prominent for Attention problems rated by parents: mean T score = 62, with a T score of 50 as the mean and 10 as the SD of the normative population and higher scores indicating more problems. Also, Social problems were commonly reported by parents: mean T score = 61. Behavioral problems that were less pronounced than could be expected from literature were Internalizing behavioral problems rated by parents (0.6 SD more problems than the healthy population), and Internalizing behavioral problems self-rated by children (0.5 SD more problems than the healthy population). All baseline group averages were significantly different from reference groups, except for psychosocial quality of life. The mean z-score for psychosocial quality of life, measured by the CHQ was -0.1 (SD 0.7; p-value 0.22).

One-year test-retest effects in the placebo group

The placebo group of the trial (n=39) provides a unique opportunity to examine one-year longitudinal changes in scores on the outcome measures. Full-scale intelligence was significantly higher after 12 months of placebo-use (table 2). This is due to an average 5.5 IQ-point increase in performance intelligence. Verbal intelligence did not improve over time. Improvements were seen on Stroop CWT scores, which were lower after 12 months, and on the Grooved Pegboard test. This is not unexpected, as these two tests have no adequate age-corrected reference data. Psychosocial health-related quality of life was .2 z-scores higher after 12 months (p = 0.045). Small reductions in behavioral problems were observed on most domains, but these were not statistically significant.

Table 2. Degree of cognitive deficits and behavioral problems in the total study population at baseline, and test-retest effects in the placebo group.

	Total study population		Test-retest effects in the placebo group only				
	Baseline	SDS	Baseline	After 12m	Change	*p*-value	Test-retest *r*
Cognitive domain							
WISC-III (IQ-points)	*n*=84		*n*=39				
- Full-scale intelligence *	83.3 (15.6)	- 1.1	82.3 (15.5)	85.4 (16.4)	3.1	.0011	.942
- Verbal IQ	86.1 (15.7)	- 0.9	83.7 (14.7)	83.6 (14.7)	- 0.1	.965	.881
- Performance IQ	83.4 (15.7)	- 1.1	84.1 (16.6)	89.6 (17.8)	5.5	.0001	.899
Rey Complex Figure Test (*z*-scores)	*n*=84		*n*=39				
- Copy	-1.4 (1.4)	-1.4	-1.6 (1.7)	-1.5 (1.4)	0.03	.915	.733
- Delayed Recall *	-2.0 (1.0)	-2.0	-2.0 (1.1)	-1.7 (1.2)	0.31	.133	.521
Stroop Color Word Interference Test *	*n*=80		*n*=37				
(seconds)	69 (42)	N/A	65 (45)	47 (27)	-17.2	.002	.777
Teacher rated school performance *	*n*=66		*n*=30				
(scale 2 – 10)	5.8 (2.3)	N/A	5.7 (2.4)	6.0 (1.9)	0.3	.459	.597
Grooved Pegboard, dominant *	*n*=84		*n*=39				
(seconds)	89 (26)	N/A	84 (23)	79 (18)	-6	.002	.814
Behavioral domain							
CBCL - Parent report (*T*-score)	*n*=84		*n*=39				
- Total problems	57.5 (9.3)	- 0.7	56.7 (9.0)	55.7 (9.2)	-1.0	.422	.627
- Attention problems*	61.9 (8.6)	- 1.2	62.0 (7.6)	60.9 (7.1)	-1.1	.330	.398
- Internalizing behavioral problems*	55.9 (10.4)	- 0.6	56.0 (10.0)	54.9 (10.6)	-1.2	.274	.793
- Social problems	61.3 (8.0)	- 1.1	61.1 (8.1)	59.2 (6.7)	-1.9	.115	.574
Youth Self Report (*T*-score)	*n*=49		*n*=24				
- Total problems	53.5 (8.8)	- 0.4	52.2 (7.2)	51.0 (9.4)	-1.2	.443	.639
- Attention problems	57.7 (7.6)	- 0.8	57.9 (8.7)	56.3 (7.6)	-1.6	.424	.642
- Internalizing behavioral problems*	54.9 (10.2)	- 0.5	52.9 (8.3)	51.7 (9.8)	-1.3	.543	.412
- Social problems	59.0 (6.7)	- 0.9	57.4 (5.0)	57.8 (6.7)	0.5	.936	.194$
Teacher Report Form (*T*-score)	*n*=82		*n*=39				
- Total problems	55.9 (7.6)	- 0.6	55.6 (8.7)	54.5 (7.9)	-1.1	.415	.538
- Attention problems	55.8 (5.1)	- 0.6	56.3 (5.0)	54.5 (4.7)	-1.7	.097	.450
- Internalizing behavioral problems	56.0 (10.6)	- 0.6	56.3 (11.2)	56.5 (11.1)	0.2	.912	.400
- Social problems	60.3 (8.2)	- 1.0	59.7 (8.2)	59.3 (8.8)	-0.4	.806	.388
Quality of life domain							
Psychosocial Health-related quality of life*	*n*=83		*n*=38				
(*z*-score)	-0.1 (0.8)	-0.1	-0.1 (0.7)	0.1 (0.6)	0.2	.042	.654

All baseline scores were significantly worse than reference groups with a p-value of <.001, except for YSR – Total problems, p-value < .01, and psychosocial health-related quality of life, p-value >.05. Higher IQ-points, z-scores or teacher rated school performance mean better performance, higher time-scores in seconds and higher T-scores mean worse performance or more behavioral problems. The changes from baseline in the placebo group show significant increases on several outcome measures. All test-retest correlation coefficients were significant with a p-value <.001, except for YSR - Social problems, p-value > .05. Values denote mean with standard deviations. * pre-defined outcome measure in NF1-SIMCODA.

Correlations between before and after measurements give an indication of test-retest reliability and/or the within-subject stability of the underlying construct.22 Poor before-after correlation coefficients would indicate that a higher number of subjects would be needed to find significant treatment effects in a randomized trial. Before-after correlations were good to excellent for Wechsler-scales (Verbal intelligence: r= .88, Performance intelligence: r = .90, Full-scale intelligence r = .94), poor for RCFT delayed recall (r = .52), acceptable for Stroop CWT (r = .78) and good for Grooved Pegboard test (r = .81). Behavioral problems reported by parents had questionable correlation coefficients for Total problems and Social problems (r = .63) but acceptable correlations for internalizing behavioral problems (r = .79). Of note, before-after correlations were low for Attention problems (r = .40), a scale that was used as an outcome measure in NF1-SIMCODA. Youth Self-report before-after correlations (available for 24 subjects in the placebo-group) were low for Internalizing behavioral problems (r= .41) and Social problems (r = .19), and questionable for Total problems (r= .64) and Attention problems (r = .64). Behavioral problems reported by the teacher showed a poor before-after correlation (r range: .39 – .54). Importantly, the majority of children changed teachers over the one-year period. Psychosocial health-related quality of life had questionable before-after correlation (r = .65).

Analysis of the correlation structure within the outcome data

Next we analyzed the correlation structure between the scores at baseline on various outcome measures. We had to consider the total sample size of 83 complete cases, allowing for a limited number of variables to be included. We included those outcome measures that were evaluated in a sufficient number of children (see Methods section for selection criteria). Table 3 shows the correlation matrix of the selected outcome measures, together with the significance levels. Of note, parent-rated Attention problems had no significant correlation to scores on the Stroop CWT, which we included as a measure of attention. The principal component analysis of these correlations resulted in two components. Table 4 shows the component loadings after rotation. The outcome measures that cluster on the same factor suggest that component 1 represents behavioral problems, and that quality of life clusters together with these behavioral problems. Component 2 represents cognitive functioning. The correlation between the two components is low (-.123). These data suggest that the performance of children in the NF1-SIMCODA trial on the cognitive outcome measures was independent from the behavioral problems reported by parents.

In addition, it shows that psychosocial quality of life scores as reported by parents, correlate much higher with behavioral problems than with cognitive deficits.

Table 3: Pearson correlations

	Internalizing behavioral problems	Attention problems	Social problems	Psychosocial quality of life	Total verbal intelligence	Total performance intelligence	Rey CFT – delayed recall	Stroop Color word test - interference	Grooved Pegboard test
Internalizing behavioural problems	1.000	**.494**	**.715**	**-.597**	-,139	-.039	-.195*	.020	.022
Attention problems	**.494**	1.000	**.539**	**-.406**	-.231*	-.077	-.153	.080	.079
Social problems	**.715**	**.539**	1.000	**-.583**	-.237*	-.057	-.108	.010	.104
Psychosocial quality of life	**-.597**	**-.406**	**-.583**	1.000	.004	-.112	-.054	-.132	-.117
Total verbal intelligence	-.139	-.231*	-.237*	.004	1.000	**.650**	**.379**	.049	-.064
Total performance intelligence	-.039	-.077	-.057	-.112	**.650**	1.000	**.469**	-.015	**-.366**
Rey CFT – delayed recall	-.195*	-.153	-.108	-.054	**.379**	**.469**	1.000	.011	-.230*
Stroop Color word test - interference	.020	.080	.010	-.132	.049	-.015	.011	1.000	.317**
Grooved Pegboard test	.022	.079	.104	-.117	-.064	**-.366**	-.230*	.317**	1.000

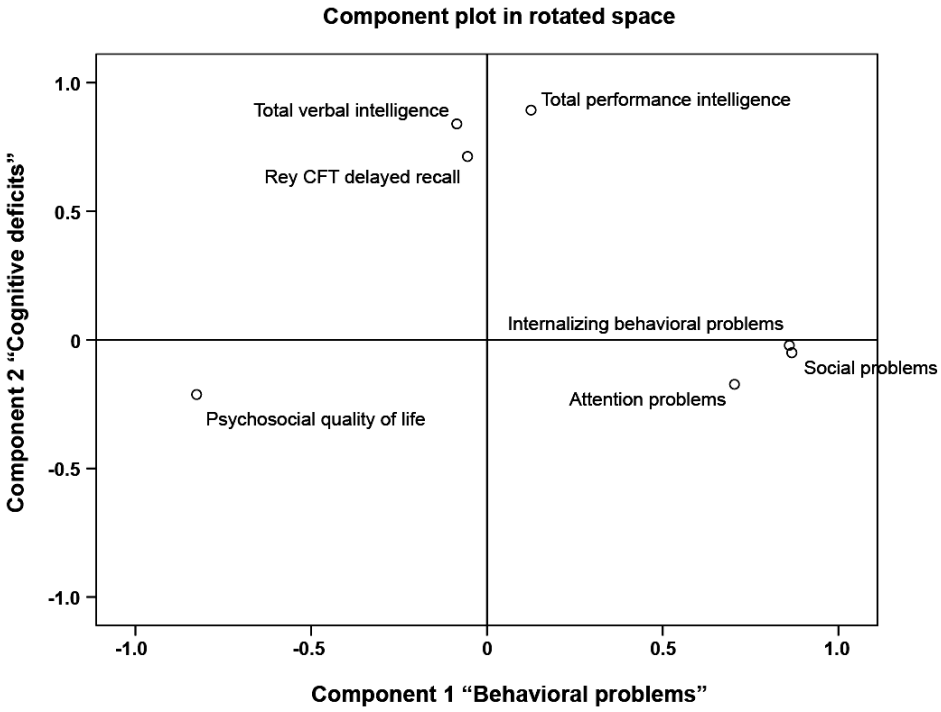
* indicates $p < .05$; ** indicates $p < .01$, bold indicates $p < .001$.

Table 4. Summary of principal component analysis for the seven outcome measures included ($n = 83$)

	Internalizing behavioral problems	Attention problems	Social problems	Psychosocial quality of life	Total verbal intelligence	Total performance intelligence	Rey CFT – delayed recall	Eigenvalues	% of variance
Rotated Component Loading									
"Behavioral problems"	**.86**	**.70**	**.87**	**-.83**	-.09	.13	-.06	2.82	40.30
"Cognitive deficits"	-.02	-.17	-.05	-.21	**.84**	**.89**	**.71**	1.97	28.11

Component loadings over .40 appear in bold.

Figure 1. Component plot in rotated space.



Discussion

We analyzed the performance of a range of cognitive, behavioral and quality of life outcome measures in a real-life clinical trial population of children with NF1 in order to improve clinical trial design of future studies.

This report confirms the broad range of cognitive deficits and behavioral problems in patients with NF1.[4, 6] As expected, the participants scored poorly on full-scale intelligence and RCFT delayed recall. In the behavioral domain, parents frequently reported Attention problems, but Internalizing behavioral problems were less prevalent in our sample than expected from previous studies.[6, 19, 23] Interestingly, social behavioral problems were a major issue in our study population, and were also correlated to loss of quality of life. Recently, much attention has been directed at the prevalence and characterization of autism spectrum disorder within the NF1-population.[24-27] One ongoing clinical trial is specifically designed to evaluate the effect of simvastatin on autism in children with NF1 (SANTA-trial, EUDRACT-number: 2012-005742-38).

The test-retest reliability analysis we performed indicated that the most reliable tests include full-scale intelligence, performance intelligence, followed by neuropsychological tests. We found evidence for a poor test-retest reliability of scores on Attention problems rated by parents. This finding indicates that the symptoms of attention problems in a given child may fluctuate more strongly than other outcomes do. Our analysis cannot discriminate between test-retest reliability (the test being imprecise) and a true high variability of Attention problems over time.[22] Attention problems are considered a key aspect of the neurocognitive profile of NF1 and have been targeted in all therapy trials so far. The low stability of Attention problems parent rating might reflect a poorly understood natural variability within the NF1-population that is not observed within the reference population. Test-retest correlations for the Attention problems scale measured weeks apart in the reference population are as high as .90[28], and long-term stability spanning 2-3 years during school age are around 0.70.[29] In a clinical sample of ADHD patients, stability of Attention problems over four years' time was 0.53.[30] Interestingly, Stroop CWT in our study has high stability over one year time and was not correlated to questionnaire-based attention problems. The indication that attention problems ratings have high intra-individual variability in NF1 warrants further prospective evaluation.

In addition, we found that behavioral problems, but not cognitive deficits, were strongly associated with psychosocial quality of life on the CHQ-PF50. This is in agreement with a previous

study, where behavioral problems were associated with reduced quality of life, but school performance was not.[19] There might be an overlap in constructs measured between the behavioral questionnaires and the quality of life questionnaire, explaining this correlation. Therefore, the CHQ-PF50 seems insensitive to issues these children face in cognition and academic achievement. Future research might focus on developing an NF1-specific health-related quality of life scale to include all items that are relevant to children with NF1, including academic achievement and cognitive performance.

The correlation between cognitive outcome measures and behavioral problems in this population of children with NF1 was not significant. Some children displayed mainly behavioral problems, whilst some only had cognitive problems. Payne et al. investigated scores on neuropsychological tests for attention in correlation with parent-rated questionnaires on working memory and attention and found at best moderate correlations between tests and questionnaires.[31] Pride et al. found that a behavioral diagnosis of ADHD predicts poorer academic achievement. [32] It is unclear at present what causes this heterogeneity. There might indeed be multiple pathways responsible for cognitive deficits and behavioral problems in children with NF1, with inter-individual differences in the relative contribution of these mechanisms.[33] Since it is yet unpredictable which neurocognitive substrates or behavioral problems will respond to treatment, it seems justified to include a broad set of outcome measures in early clinical trials, covering cognition, behavior, and quality of life.

Other researchers have commented that outcome measures should focus on transferring tasks from mouse models to humans.[34-36] Paired-associate learning (PAL), a subtest of the CANTAB neuropsychological testing battery, has been implemented in a running clinical trial of Lovastatin in NF1, based on its supposed similarity to the visuospatial learning in the mouse model.[35] Although the NF1-population is indeed affected on this particular task, it remains unclear what the clinical relevance is of such tasks. In a similar fashion, it might be tempting to translate the Morris Water Maze task to a human maze-like test, as was done in one study.[36] In our opinion, it is important to respect the ecological differences in behavior between mice and children. Drugs that improve performance of children on a visuospatial learning task, but do not improve clinically relevant patient-reported outcomes such as behavioral problems, academic achievement and quality of life, are of purely academic interest.

Although the results of the current analysis are specific for NF1, the approach of validating outcome measures for cognitive research can well be used in other disorders. It is important to scrutinize the few trials that have been completed in order to guide future clinical trial design. In conclusion, this study highlights the variability of the neurocognitive profile of NF1 and demonstrates the need to include outcome measures on a variety of cognitive and behavioral domains in clinical trials.

Acknowledgements

Other members of the NF1-SIMCODA study group are dr. M. Renard, dr. R. Oostenbrink, dr. A. Vogels, dr. M.C.Y. de Wit, M.J. Descheemaeker, Y. Vergouwe and C.E. Catsman-Berrevoets. The authors thank B. Manai for his assistance in data collection.

References

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

2. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 1989;26:704-711.

3. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81-88.

4. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005;65:1037-1044.

5. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol 2008;23:1002-1010.

6. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

7. Krab LC, de Goede-Bolder A, Aarsen FK, et al. Motor learning in children with neurofibromatosis type I. Cerebellum 2011;10:14-21.

8. Marchuk DA, Saulino AM, Tavakkol R, et al. cDNA cloning of the type 1 neurofibromatosis gene: complete sequence of the NF1 gene product. Genomics 1991;11:931-940.

9. Xu GF, O'Connell P, Viskochil D, et al. The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell 1990;62:599-608.

10. Cui Y, Costa RM, Murphy GG, et al. Neurofibromin regulation of ERK signaling modulates GABA release and learning. Cell 2008;135:549-560.

11. Costa RM, Federov NB, Kogan JH, et al. Mechanism for the learning deficits in a mouse model of neurofibromatosis type 1. Nature 2002;415:526-530.

12. Shilyansky C, Lee YS, Silva AJ. Molecular and cellular mechanisms of learning disabilities: a focus on NF1. Annu Rev Neurosci 2010;33:221-243.

13. Li W, Cui Y, Kushner SA, et al. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. Curr Biol 2005;15:1961-1967.

14. Brown JA, Emnett RJ, White CR, et al. Reduced striatal dopamine underlies the attention system dysfunction in neurofibromatosis-1 mutant mice. Hum Mol Genet 2010;19:4515-4528.

15. Wozniak DF, Diggs-Andrews KA, Conyers S, et al. Motivational disturbances and effects of L-dopa administration in neurofibromatosis-1 model mice. PLoS One 2013;8:e66024.

16. Omrani A, van der Vaart T, Mientjes E, et al. HCN channels are a novel therapeutic target for cognitive dysfunction in Neurofibromatosis type 1. Mol Psychiatry (in press 2015).

17. van der Vaart T, Plasschaert E, Rietman AB, et al. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol 2013;12:1076-1083.

18. Krab LC, de Goede-Bolder A, Aarsen FK, et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008;300:287-294.

19. Krab LC, Oostenbrink R, de Goede-Bolder A, Aarsen FK, Elgersma Y, Moll HA. Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior. J Pediatr 2009;154:420-425, 425 e421.

20. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ 2001;323:1123-1124.

21. Dekker MC, Koot HM, van der Ende J, Verhulst FC. Emotional and behavioral problems in children and adolescents with and without intellectual disability. J Child Psychol Psychiatry 2002;43:1087-1098.

22. Spencer FH, Bornholt LJ, Ouvrier RA. Test reliability and stability of children's cognitive functioning. J Child Neurol 2003;18:5-11.

23. Dilts CV, Carey JC, Kircher JC, et al. Children and adolescents with neurofibromatosis 1: a behavioral phenotype. J Dev Behav Pediatr 1996;17:229-239.

24. Plasschaert E, Descheemaeker MJ, Van Eylen L, Noens I, Steyaert J, Legius E. Prevalence of autism spectrum disorder symptoms in children with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2014.

25. Garg S, Green J, Leadbitter K, et al. Neurofibromatosis type 1 and autism spectrum disorder. Pediatrics 2013;132:e1642-1648.

26. Garg S, Lehtonen A, Huson SM, et al. Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. Dev Med Child Neurol 2013;55:139-145.

27. Garg S, Plasschaert E, Descheemaeker MJ, et al. Autism Spectrum Disorder Profile in Neurofibromatosis Type I. J Autism Dev Disord 2014.

28. Verhulst FC, Van der Ende, J., Koot H.M. Handleiding voor de CBCL/4–18 [Dutch manual for the CBCL/4–18]. Rotterdam: Academic Medical Center Rotterdam/Erasmus University, Sophia Children's Hospital, Department of Child and Adolescent Psychiatry, 1996.

29. Rietveld MJ, Hudziak JJ, Bartels M, van Beijsterveldt CE, Boomsma DI. Heritability of attention problems in children: longitudinal results from a study of twins, age 3 to 12. J Child Psychol Psychiatry 2004;45:577-588.

30. Biederman J, Monuteaux MC, Greene RW, Braaten E, Doyle AE, Faraone SV. Long-term stability of the Child Behavior Checklist in a clinical sample of youth with attention deficit hyperactivity disorder. Journal of clinical child psychology 2001;30:492-502.

31. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. Child Neuropsychol 2011;17:313-329.

32. Pride NA, Payne JM, North KN. The impact of ADHD on the cognitive and academic functioning of children with NF1. Dev Neuropsychol 2012;37:590-600.

33. Diggs-Andrews KA, Gutmann DH. Modeling cognitive dysfunction in neurofibromatosis-1. Trends Neurosci 2013;36:237-247.

34. Acosta MT. Challenges of cognitive research in neurofibromatosis type 1. Lancet Neurol 2013;12:1040-1041.

35. Payne JM, Barton B, Shores EA, North KN. Paired associate learning in children with neurofibromatosis type 1: implications for clinical trials. J Neurol 2013;260:214-220.

36. Ullrich NJ, Ayr L, Leaffer E, Irons MB, Rey-Casserly C. Pilot study of a novel computerized task to assess spatial learning in children and adolescents with neurofibromatosis type 1. J Child Neurol 2010;25:1195-1202.

37. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Dev Med Child Neurol 2002;44:164-170.

38. Acosta MT, Kardel PG, Walsh KS, Rosenbaum KN, Gioia GA, Packer RJ. Lovastatin as treatment for neurocognitive deficits in neurofibromatosis type 1: phase I study. Pediatr Neurol 2011;45:241-245.

39. Mainberger F, Jung NH, Zenker M, et al. Lovastatin improves impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1. BMC Neurol 2013;13:131.

40. Lion-Francois L, Gueyffier F, Mercier C, et al. The effect of methylphenidate on neurofibromatosis type 1: a randomised, double-blind, placebo-controlled, crossover trial. Orphanet J Rare Dis 2014;9:142.

CHAPTER 8.

Worries and needs of adults with neurofibromatosis type 1 and parents

Rietman AB, Van Helden H, Both PH, Taal W, Legerstee JS, Van Staa AL, Moll HA, Oostenbrink R, Van Eeghen AM

American Journal of Medical Genetics part A 2018;176:1150-1160

Abstract

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder associated with lifelong tumor growth propensity and neurocognitive impairments. Although follow-up of adults with NF1 often focuses on tumor growth, follow-up of cognitive or social problems and other NF1-related comorbidity is often not a part of standardized care. In order to provide optimal care services for these patients, we explored the care needs of adults with NF1. A qualitative study was performed using semi-structured group interviews, exploring worries and care needs in medical, psychological and socioeconomic domains, also focusing on the transition from pediatric to adult care. Four focus groups were conducted, including young adult patients, patients over age 30, and parents of young adult patients. In total, 30 patients and 12 parents participated. Data were transcribed verbatim and analyzed by computerized thematic analysis. Themes were organized using the WHO International Classification of Functioning, Disability, and Health (ICF). Results indicated many and diverse worries and care needs both during the transitional period and in adulthood in medical, mental health, and socioeconomic domains. Worries could be categorized into thirteen themes. Parents reported high stress levels and difficulties with their parental role. Participants expressed the need for more information, access to NF1 experts, daily living support, care for mental health and socioeconomic participation, and closer communication between healthcare providers. In conclusion, worries and needs of patients and parents underline the importance of multidisciplinary follow-up and continuity of care during and after the transitional period. Additionally, parental stress requires more attention from care providers.

Introduction

Neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant neurocutaneous disorder with an estimated birth incidence of 1/2700 [1]. Approximately 40 to 50% of the cases are caused by a de novo mutation in the NF1 gene [1, 2]. Clinical features of NF1 include multiple café-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas and iris Lisch nodules [3]. Serious complications of NF1 include different types of tumor formation, such as central nervous system gliomas and plexiform neurofibromas, with a risk of evolving into malignant peripheral nerve sheath tumors (MPNST's) [4] for which guidelines for neuro-oncological follow-up are available. However, although neuropsychiatric and psychosocial problems persist into adulthood, currently these are often not routinely addressed in adults.

Learning disabilities occur in at least 50% of children with NF1, making cognitive problems the most common complication to affect the quality of life in this group [5]. Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and sleep disturbance are also highly prevalent [6-8] and can persist throughout life [9-11]. Furthermore, patients with NF1 are at risk for psychosocial problems. In adolescence and adulthood, the dermatological and neuronal tumor phenotype can exacerbate in a period in which appearance, acceptance, and social inclusion are of great importance [12, 13]. Additionally, the impaired socialization, low self-esteem and poor interpretation of social cues reported in children with NF1 [14] may limit social participation in adulthood. Even when adults with NF1 receive care for the tumor growth phenotype, appropriate care for other NF1-related morbidity is often not part of standardized care [15].

For patients with NF1, international healthcare guidelines advise multidisciplinary follow-up including evaluation of tumor growth, dermatological manifestations, and neuropsychiatric disorders [16, 17]. Although pediatric patients often receive and adhere to this multidisciplinary care, studies show that young adults with NF1 may have poor access to healthcare, limited disease knowledge, and are often lost to follow-up. At the same time, they have a high complication rate and neuropsychiatric and socioeconomic problems persisted or worsened [18]. Adult patients with NF1 experience decreased quality of life [19] and they require developmentally appropriate care [15].

Thus far, limited data are available on the full scope of worries and health care needs of young adults and adults with NF1 and their parents. Previous qualitative studies have focused on the impact of NF1 in adulthood, for instance, addressing the effects of plexiform neurofibromas [20], health and well-being, quality of life, and transition to adult care [12, 21-23]. The aim of the current

study was to provide more information on the full spectrum of worries and care needs in medical, psychological, social, and economic domains of adults with NF1 and parents of patients with NF1. Using patient-driven data, we formulate recommendations for health care providers (HCP) in order to optimize health care for this vulnerable patient group.

Materials and methods

A qualitative design with semi-structured group interviews was used to obtain in-depth data on worries and care needs of patients and their parents. The full spectrum of care needs was explored, including medical, psychological, social and societal domains, and contextual factors. The COREQ (Consolidated criteria for reporting qualitative studies) checklist was used as a reporting framework for this qualitative study [24].

Participants

Convenience sampling was performed in close cooperation with the NF1 patient association of the Netherlands (NFVN). Young adults (18-30 years) and older adults (30-67 years) with NF1 and parents of patients with NF1 were invited to join focus groups, which were conducted on April 16, 2016, at a conference center in the Netherlands after the annual meeting of the NFVN. This annual meeting is generally visited by 50 to 100 patients, parents of patients and professionals. The invitation was part of the agenda that was sent to all members of this association. Inclusion criteria for the patients were that they must be 18 years of age or older, and have a diagnosis of NF1 (as stated by the participating members, not necessarily confirmed by DNA testing). The inclusion criterion for parents was having a child with NF1 who is now an adult. Participation of parents was not dependent on their child's participation or vice-versa.

Participants were divided into four focus groups: 1) patients aged 18 to 30 years, 2) parents of patients aged 18-30 years, 3 & 4) two groups of patients and parents of patients aged over 30. The cut-point of 30 years was based on the European Commission definition of 'youth and young people' [25], evidence that neurodevelopment continues up to the age of 30 years old, and clinical experience that the transitional period can be protracted in patients with neurodevelopmental disorders. Both groups 3 and 4 were mixed groups of parents and patients, who indicated they wanted to join the groups together. In total, 12 parents participated, including four fathers and eight mothers.

Data collection

Focus groups were 90 minutes in length and were moderated by a pediatrician (RO), an intellectual disability physician (AE), and two psychologists (AR, JL). Moderators were specifically allocated to ensure they had no treatment relationships with participants. Prior to the focus group, moderators received training to ensure consistency across interviews. Two observers (HH and PB) joined the focus groups.

Semi-structured interviews contained previously drafted questions and probes on worries and needs in medical, psychological, and socioeconomic domains (see Table 1). Participants were explicitly asked to discuss the transitional phase between pediatric and adult care. In the Netherlands, the transition from pediatric to adult health-care usually occurs at approximately 18 years of age[26].

Table 1. Abbreviated interview guide

Key questions: **1) What are your worries about…** **2) What are your care needs for…**	**Probes**
Transition from pediatric to adult care?	Transition to adult health care, change in physician, transition to adult life, transition to work, independent living
Medical issues?	Symptoms, NF1-related care, medication, care consultations
Psychological and behavioral issues?	Sleeping problems, ADHD, ASD, depression, anxiety
Social life?	Friendships, romantic relationships, family, family planning, loneliness, sexuality
Work and daily activities?	Work, school, independence, finances, daily living
Paramedical issues?	Language problems, nutrition, motor skills

Data analysis

Focus groups were digitally recorded and transcribed verbatim. Transcripts were imported into the qualitative software package ATLAS.ti 6.2 [27]. Thematic analysis [28] was selected for its theoretical freedom and yield of rich and detailed account of data.

All transcripts were reviewed and coded by a member of the research team (HH). Initial codes were based on the overall subject of a text fragment. During analysis, initial codes were

modified, expanded, or merged as new issues emerged. Decisions about the codes were made based on the most complete representation of the data. Subthemes were merged where possible. To enhance validity, the coding process and the emerging themes were continually discussed with two co-investigators (PB, AE), and in an additional meeting with other co-investigators themes were discussed until consensus was reached.

After obtaining a consensus on the open coding, worries and care needs were organized based on the ICF framework. The ICF is a classification of health and related domains, published in 2001 by the World Health Organization [29], and describes impairments of body functions and structures, activity limitations, participation restriction, and environmental factors. It is used as a framework to express health and disability using individual and population measures and has been used for holistic evaluation and interpretation of NF1-related disabilities in pediatric patients [30]. A valuable contribution of the ICF classification is the emphasis on the effects of health issues on activities and social and economic (socioeconomic) participation. Socioeconomic participation is defined as a person's involvement in a life situation and the socioeconomic domain represents the societal perspective of functioning. The theme 'parental stress' was classified as an environmental factor for the patient, since parents are part of the environment they live in. 'Problems during transition phase' were also considered an environmental factor since the current healthcare infrastructure appeared to contribute to these problems.

The education of patients was classified according to the international classification of education (ISCED 2011) [31].

Ethical approval

This study was approved by the medical ethical review committee of the Erasmus Medical Centre (ref. MEC-2016-532). For all participants and recordings, informed consent was obtained and a formal review and waiver of the MEC was given.

Results

Participants

Forty-two participants were included; 30 patients and 12 parents (see Table 2 for patient characteristics). The age of patients ranged from 18 to 67 years, while the age of parents ranged from 54 to 75 years. The NF1-mutation status of parents was unknown. After transcription and coding, 13 major themes were identified and classified using the ICF (Table 3 provides an

overview). The ICF-framework proved to be a useful tool in organizing the diversity of worries and needs ensuring an overview of both functional impairments and their consequences in daily life. Detailed results of the analysis of the transcript are provided below. The addition of new codes diminished greatly during analysis, suggesting data saturation.

Table 2. Description of the study sample

	Focus groups			
Characteristics	**1. Patients 18-30**	**2. Parents of patients 18-30**	**3 and 4. Parents and Patients 30+**	**Total**
Patients (*N*)	12	-	18	30
Parents (*N*)	-	7	5	12
Age of *patients* in years (*Median, interquartile range*)	24.5 (22.3-29.5)		53.5 (36-59.5)	36.0 (27.3-55.5)
Gender of *patients*:				
Female *N* (%)	8 (67)		6 (33)	14 (47)
Male *N* (%)	4 (33)		12 (67)	16 (53)
Highest level of education of the patient, *N* (%):			[b]	[b]4
Primary- lower secondary (ISCED 1-2)[a]	1		3	15
Upper- post-secondary (ISCED 3-4)	8		7	10
Bachelor- university degree (ISCED 5-7)	3		7	

[a] ISCED: International classification of education; [b] information on education of 1 patient missing

Table 3. ICF categories, themes, and corresponding codes

ICF Classification	Themes	Codes
Impairment of body functions and structures	Mental health problems	Anxiety, worries in many areas, symptoms of depression, problems with emotion and mood regulation, ADHD symptoms, ASD symptoms, problems coping with having NF1[a], problems with self-acceptance[a]
	Worries about the future	Worries about future symptoms and prognosis
	Cognitive deficits	Learning disabilities, language and speech problems
	Physical problems	Sleeping problems[a], fatigue, headache, pain, growth of neurofibromas, unexplained physical complaints
	Visibility of disability	Problems with visibility of NF1, focus of others on external features[a]
Activity limitations & participation restriction	Limitation of independence	Difficulties adjusting life to complications of NF1[a], difficulty reaching independence, patient does not recognize and/or seek help for NF1 symptoms[b], problems with planning[a] and organizing
	Social deficits limit participation	Lack of self-confidence[a], trouble with initiating and maintaining social and romantic relationships, loneliness
	Family planning difficulties	Worries about the risk of passing NF1 to offspring[a], worries about medical procedures to have children, uncertainty about obtaining a relationship
	Limitations with work	Unable to work full time, overestimation, difficulties with finding and keeping work[b]
Environmental factors	Required support in daily life	Support of parents, support of network, support of patient association, involvement of health care professionals in living and working arrangements
	Problems during transition process	Protracted transition[b], buddy needed in transition time, no consultation between doctors, unsuccessful transition
	Limited access to adequate care in various domains	Knowledge of NF1 absent in doctors, lack of mental health care[a], difficult to find an NF1 expert[b]. Need for one contact person instead of multiple healthcare providers[a], need for communication between health care providers, need for multidisciplinary care[a], need for family planning care[a], support for parents[b], need for more social and societal assistance
	Parental stress	No acknowledgment of worries of the parent by care providers[b], much time spent on assistance and administration[b], confusion about parental role[b], decreased quality of parent-child relationship[b]

[a] Mainly discussed by patients

[b] Mainly discussed by parents

Impairment of body functions and structures

Mental health problems

High levels of anxiety and stress were broadly discussed, such as fear of failure, social anxiety, and fears and worries about the future. Symptoms of depression were also discussed in all focus groups, as several patients reported needing antidepressants and psychological consultation. Both patients and parents noted problems with emotion and mood regulation, leading to anticipatory stress and frustration by family members.

"Anxiety is always present, you know. Fear of new situations, and also fear of meeting new people. I see it in my son, even when he needs to go into a new store. So every time he goes somewhere new for the first time, he wants me to join him."– Parent 18-30

Difficulties with self-acceptance and coping with the disease were widely present. Especially patients in the 30+ focus groups, who mentioned that it would have been helpful if psychological care had been offered. Various patients noted that the disorder of NF1 itself limited their coping skills: fatigue, anticipatory stress, and a depressed mood made them feel less resilient.

Worries about the future

The unpredictable course of NF1 was a major concern of patients. Patients worried about future symptoms and prognosis, future loss of functions, future surgery, future aesthetic problems, malignant transformation of neurofibromas in the future, obtaining relationships, and achieving independence.

"It is just that you don't know how it will be. Really everything is worrisome." – Patient 18-30

Cognitive deficits

Language and speech problems were mentioned and some adults received speech therapy. Not many cognitive deficits or learning problems were presented as worries, although their dependence on others was often mentioned. Some parents had the impression that cognitive development stopped or slowed during the transition period because their children reached independence much later than their peers.

"... That's where I have question marks. I wonder if development in those children, in young adults under age 30, if there is still progress." – Parent 18-30

Physical problems

There was great diversity in the experienced physical problems. Sleeping problems, fatigue, headache, and limited motor skills often expressed as 'clumsiness' had a major impact on daily life. Fatigue and headaches had a large effect on the ability to work full time and to participate in as many activities as peers. Various sleeping problems were reported as a concern; difficulty falling asleep, difficulty staying asleep, difficulty waking up and need for sleep medication. Furthermore, the growth of neurofibromas was mentioned as a major cause of frustration, because of possible malignant transformation and changing appearance. Symptoms mentioned by a small group of patients were pain, back pain, and scoliosis. Limited motor skills had a more indirect impact on the lives of the patients, for instance being unable to cycle or swim.

Visibility of disability

Patients noted being watched, stared at, and/or insulted in public places because of their cosmetic problems. The visibility of the disease caused questions from outsiders which were perceived as annoying, for example, questions about contagiousness.

"It was hinted that I had to leave the pool because others had problems with me being in the pool." – Patient 30+

Particularly the younger patients were annoyed about NF1-portrayal in media, for example only the worst cases being shown on television or the internet, resulting in a false perception of NF1.

"There was a documentary also about (person's name), and it's always about getting the worst, very worst, the worst of all ... and showing the most severe [cases]…" – Patient 18-30

Activity limitations & participation restriction

Limitation of independence

Parents and patients mentioned their worries about achieving independence. Parents reported that their children with NF1 took little initiative. Young adults emphasized that achieving independence was delayed; some patients wanted to complete school before moving out of their

parent's house. Those who lived independently stated that they needed assistance in housekeeping, planning, and organizing. Patients had trouble asking for help, resulting in having to wait for people offering assistance. Additionally, patients encountered problems adjusting their lives to their limitations caused by NF1, for example planning too many activities while at the same time having limited energy.

"I'm having a hard time becoming independent, and it's very scary to separate from my parents and to do it all by myself." – Patient 18-30

Many parents remained in the coordinating role regarding medical affairs and participated in visits with medical specialists, claiming that patients did not recognize and seek help for NF1 symptoms.

Social deficits

Loneliness and trouble initiating and maintaining social and romantic relationships were the main social problems. Some of the young adults stated to have had social skills training in the past. Furthermore, patients feared a lack of understanding of NF1 in new social contacts. Both patients and parents mentioned that friendships were complicated by limited understanding of the disorder in their environment.

"Yes, obtaining friendships is difficult because she [my daughter] sometimes behaves a bit awkward." – Parents 18-30

Especially among patients between 18-30, feelings of insecurity and low self-esteem were reported. They felt that they were 'different' from others and wanted to be 'normal'. Many patients were still trying to cope with bullying in their past and some patients even mentioned this prior bullying "still influenced their current social skills".

Family planning difficulties

There were many worries regarding family planning. Patients appeared to be informed that they could pass NF1 to their offspring, but discussed their need for timely and adequate information and care on this issue. Some of the patients mentioned the desire to have children but felt uncertain about obtaining a relationship which would allow for that in the future.

"I want children, but do not want to inflict upon them the life that I'm leading, […] so yes, you have to go into that trajectory, but who with, and how, and adopting is an option, but then you can't

give birth, and yes, I'm twenty now and I do not have a partner, and I'm getting older…"Patient 18-30

Limitations with work

For cognitively high-functioning patients (ISCED levels 5-7), fatigue was a large cause of problems at work. They felt unable to work full-time, but the reduction of working hours was not always allowed by their employers. Patients mentioned the need for assistance with employment matters, for example: obtaining a suitable job, obtaining a permanent contract, overestimation of abilities, lack of understanding of disabilities, and unequal treatment at work. A job coach or specific organizations were often deployed, but not always successfully. Parents indicated the need for involvement of health care providers in living and working arrangements.

"Fatigue, headaches … there is zero understanding …" – Parents 18-30

"Actually, in my view, a coordinating physician should refer to rehabilitation doctors earlier, or that for the home/work situation a medical advice is provided, about how to proceed with such a child…" – Parents 18-30

Environmental factors

Required support in daily life

Parents and patients all mentioned the need for support and recognition, and many of them found this in peer groups of the national patient association. Also, they appreciated people in their direct networks showing interest in NF1, both in real life and in social media networks.

"… in the peer group, we recognize each other there, fortunately, we are very happy with the patient foundation because we feel supported." – Parents 18-30

Problems during transition process

Many of the patients declared that the transition to adult health care had been hampered by a lack of communication about the transition to adult care, lack of organization of adequate follow-up, lack of consultation between physicians, and lack of referral to expert care. Often, patients were referred back to their general practitioner (GP) for adult care. Parents noted that counter to their expectations, care needs increased after becoming 18.

Limited access to adequate care

A number of patients noted that they appreciated when their GP was closely involved. Patients noted the lack of communication and consultations between physicians. Generally, it was very difficult to find physicians with knowledge and experience with NF1, and often second opinions were required. Patients from outside NF1 expertise centers were not referred to appropriate adult care by their GP's or pediatricians. Psychological support during intensive treatments (for example facial surgery) was not often offered but mentioned as a care need by various patients. Parents felt that their child received inadequate care if parents were not involved.

"Some physicians, they didn't know the disorder and they had to sometimes 'google' during the consultation, and that I find absolutely unacceptable, personally." – Patients 18-30

Patients and parents indicated a need for one easily accessible contact person for NF1-related questions, surrounded by a multidisciplinary team. Also, they were in need of family planning care, social assistance and community support, and support for parents. During the focus groups, the question was raised about whether the expertise center could provide information about NF1 to employers, health insurance companies, and social security offices. These organizations have a lack of knowledge about NF1 and patients would benefit if they would have more information. Interestingly, parents noted that short-term thinking was helpful for their child, because of their slower development and the unpredictable course of NF1. As remarks about possible long-term effects of NF1 were not found to be useful and unnecessarily stressful, parents also advised professionals surrounding the NF1-patient to use 'short-term thinking' with short-term recommendations.

NF1 related stress in parents

Parents were particularly concerned about their children not recognizing NF1-related symptoms such as (growth of) neurofibromas, not seeking health care, not receiving proper transitional care, and losing their child to the complications of NF1. Parents worried about the slow development of independence and the vulnerability of their child (e.g. risking abuse). Many parents reported high stress and fatigue levels due to their persistent coordinating role in the lives of their children - spending much time with the planning, organization, and administration of daily life and medical issues. Some parents even acted as a legal representative. Consequently, by having the coordinating role, the question arose: "Who will take care of our child when we are no longer able

to do so in the future?" Parental concerns were generally not acknowledged or addressed by health care providers or people in their environment, leading to increased stress.

"… Listen to us, really hear us, even when it seems exaggerated" – Parents 18-30

Discussion

This study offers patient- and parent-driven data on worries and care needs of adult patients with NF1, with an emphasis on the transitional period. Worries emerged from a broad spectrum of areas, ranging from physical and mental health to areas of social and occupational participation, and transition. This enabled us to formulate recommendations for transitional and adult care.

Physical health

Physical symptoms such as fatigue, headaches, sleeping problems, and pain had a large effect on daily life and were the cause of many worries and medical consultations. Most of these generally non-specific symptoms have been reported in children, adolescents, and adults with NF1 [7, 32-34]. Although tumor growth must be excluded, further clinical evaluation often indicates that these physical complaints may be associated with NF1, but also with mental health, lifestyle, or problems at work. Patients pointed out they wished to know whether these complaints were associated with NF1. Since these complaints have a great impact on quality of life, referral to psychological or occupational care is warranted to cope with these symptoms. Different levels of care may help to answer these questions regarding the role of NF1 in any of these problems. A healthcare model with an NF1 expertise center, coordinating NF1-specialists, and several regional treatment centers (a 'hub-and-spoke' model, the way complex NF1 services are organized in the United Kingdom) may facilitate close cooperation of GP's with a center that offers the appropriate level of care.

Mental health

Although many psychological worries were reported, most participants noted a lack of routine assessment of these problems and experienced difficulties finding appropriate evaluation and treatment. Fears and worries about the future occurred very frequently on many different topics and potential growth of neurofibromas was especially worrisome to the participants. Symptoms of depression and anxiety are frequently found in patients with NF1 [35, 36] which may be related to the

risk of development of malignancies, as is the case in patients at risk for breast and colon cancer [37, 38]. In NF1, MPNST is the most commonly found malignancy with a lifetime risk of 8-13% in NF1[39]. In the current study groups, problems with self-acceptance, low self-esteem, and limited socioeconomic participation also seemed associated with the NF1 related cosmetic burden [19] and mental health problems.

Although primary concerns with cognitive deficits were not reported, limited independence and poor social skills were worries of both patients and parents, and symptoms of ADHD and ASD were broadly described. Although more elaborately documented in children with NF1, neurocognitive deficits also result in significant limitations in adults with NF1 [14] and our results underline the presence and burden of these deficits throughout life.

Activities and participation

Patients expressed frustrations about their inability to function independently, limiting their socio-economic participation. Difficulties adjusting their life to the complications of NF1 and asking for help, problems with organizing and planning daily life, and problems with relationships and work were widespread. Poor social skills, reported in children [40] and adults with NF1[41], affect the lives of adult patients, manifesting as problems initiating and maintaining social and romantic relationships. Also, negative reactions from others to visible differences in appearance may affect self-esteem and the forming of these social and romantic relationships [22]. Participants experienced problems with finding and maintaining work, and problems with employers. During the interviews, inadequate socioeconomic participation and loneliness appeared to be associated with psychological complaints - which has been reported before in teenagers and young adults with NF1 [42, 43].

Family planning was an important theme, especially for young adults, which is in line with previous research [44]. Patients stated that they would want to have children without NF1 and that additional and timely education about genetics and reproduction was needed, although patients could not agree on the age at which this information should be given. This indicates that health care providers should make patient-specific decisions on the appropriate timing and level of detail of this information.

Environmental factors

Generally, adult patients and parents seemed to be well informed about NF1, but they often noticed a lack of knowledge in people in their direct environment. Both patients and parents

experienced limitations in their environment, such as lack of appropriate health care, lack of multidisciplinary care, lack of family care, and inadequate support from family, social networks, and employers.

Parental stress

Parents of patients have previously participated in research to elucidate the impact of NF1 on their children [45], yet the impact on parents themselves has not been described yet. In our study, parents of young adults reported many worries, high stress levels, and little attention from health care providers for their complex parental role. Since the GP is often well informed about family issues, she/he may have a crucial role in referring to the appropriate type of support and mental health care in the community.

Parental stress has been described in other pediatric cohorts with neurodevelopmental syndromes or autism [46-48]. In children with NF1, mothers reported higher parenting stress than the mothers of typically developing children [49]. The uncertainty of tumor progression may increase anxiety in both patients and parents of patients with NF1. In future research, the contributing factors to parental stress should be explored more fully, to identify parents at risk and to provide targets for prevention and treatment. In addition to parental stress, future research should also address the stress of other members of families with NF1.

Implications for transitional care

The transitional period from pediatric to adult care is known to be a challenging phase for patients with NF1 and their parents [12, 18], which was confirmed by our participants. For many patients, this transition did not proceed well. Although expert adult care for the tumor phenotype was often accessible, finding NF1 experts in other domains was difficult. The neuropsychological deficits that frequently occur in patients with NF1 may decrease their self-care and organizational capabilities, which puts them at risk for problems during the transition to adult care [12]. At this age, as is also the case in our sample, differences between parent- and patient-reported worries underline that both parents and young adults should be involved in the transitional process.

Previous studies on the transitional stage in patients with special needs, such as intellectual disabilities or chronic disorders, have shown that many adolescents experience significant problems with the continuity of care during the transition to adult health care [50-52]. Often, after years of periodic check-ups by the pediatrician before adolescence, patients discontinued clinical evaluations or did not have contact with any health care professionals [18, 53]. In our study, adult

patients expressed a need for well-informed, accessible, and multidisciplinary NF1 expertise in close communication with the patient's local network and care providers. Continuous 'chronic' care before, during, and after transition [54] could be facilitated if these specialists could also be 'generalists' in adult care for people with neurogenetic disorders in the way pediatricians are in pediatric care [55].

Implications for adult care

From the worries mentioned above, conclusions can be drawn regarding the organization and the content of care provisions. These findings expand on current recommendations for the management of NF1 [56]. Suggestions for clinical practice are listed in Table 4: 'Addressing health care needs during NF1 consultation'.

Table 4. Improving clinical practice: Addressing health care needs during NF1 consultation

Care needs	Screen patient for	Provide
Follow-up by NF1-experts	Complexity and co-morbidity. Local network of health care providers.	Easily accessible NF1 expert. Multidisciplinary NF1 expertise center for periodic screening of children, adolescents, and adults. Close communication between GP, care professionals, and NF1-experts.
Information and education on tumor phenotype and prognosis	Tumor phenotype according to current guidelines, including tumor growth, pain, loss of function. Knowledge of tumor-related symptoms, prognosis.	Regular monitoring of tumor-related symptoms. Patient information and education. Referral to patient association, websites, and brochures.
Other physical symptoms	Fatigue, sleeping problems, headache, medication side effects. Somatic comorbidity.	Exclude tumor growth; identify appropriate care in collaboration with GP. Inform about NF1-related complaints. Psychomotor therapies. (Neuro)psychological evaluation and treatment.
Mental health problems	Worries, social problems, isolation, feelings of loneliness, depressive symptoms including suicidal thoughts, ADHD, ASD.	Referral to community support by GP. (Neuro)psychological and psychiatric evaluation and treatment, peer groups, social worker[a].
Social participation Economic participation Daily life	Involvement of friends and family, social activities, romantic relationships, support network. Suitable work or daytime occupation. Independence, needs for assistance, financial space. Planning and organizing daily life, self-care, chores.	Evaluation of social and occupational skills. Social worker.[a] Information and advice for employers, insurance companies, and social services. Occupational medicine, occupational therapy.
Family planning	Knowledge of birth control methods, inheritance, family planning options, pre-conception consultation.	Inform GP, refer to clinical geneticist, gynecologist, psychologist.

Need for information, education, and support for patients, parents, siblings, partners, GP's, employers, and network	Knowledge of symptoms, care infrastructure, prognosis.	Accessibility for consultation. Patient education. Care guidelines for GP. Information brochures for friends/family, teachers, employers. Communication during transitional phase. Information or guidelines for care providers, periodic letters with advice.
Reduction parental stress, especially in parents of young adults	Screen both parent/caregiver and patient, if necessary in separate consultations.	Address parental concerns. Increase support for patient in daily life to alleviate parental responsibilities. Support for parent through GP, social services or psychologist.
Continuity of care during transitional period	Screen for all care domains starting at age 14.	Close communication between NF1 HCP, GP, and social worker until appropriate work, living, and medical care arrangements are in place.

[a] Social worker is used here, but may be substituted or supported by ambulatory help, informed volunteers or other local care where available.

In all groups, next to a local network of health care professionals including a GP, a desire for multidisciplinary expertise on adults with NF1 was expressed, to obtain treatment and information on all domains. As our results suggest, this expertise team should communicate closely with local health care providers and would be responsible for diagnosis, timely follow-up, second opinions, education, and assistance for the patients, parents, and even the socio-economic network. Screening and follow-up for mental health problems should be included in routine follow-up, as this patient group is at risk for psychiatric morbidity [11, 35, 36, 41, 57]. In practice, this implicates that individuals with NF1 should be offered structured care, including an accessible leading NF1-expert team who routinely screens for physical and mental health and for limitations in participation in social, occupational or other meaningful daily activities. Prevention and early intervention of mental health problems can be efficient and cost-effective [58] and will ultimately improve socioeconomic participation and quality of life.

Since this study offered us a clear view of worries and care needs within patients with NF1 and parents of patients with NF1, comparisons across different genetic neurodevelopmental syndromes might help to find common factors and to contrast these findings to neurocognitive, neurobehavioral, and environmental factors.

The organization of multidisciplinary and multilevel care requires a method for severity assessment that includes the full impact of NF1 on all ICF domains, including limitations in activities and participation. Although the Riccardi scale for disease severity [59] has frequently been used to assess impairments [60-62], many worries and healthcare needs of our respondents are not addressed by this scale, since it mainly focuses on disease characteristics at a somatic level. This suggests there is a need for assessing the full impact of NF1 on all ICF domains, including limitations in activities and participation. In Tuberous Sclerosis Complex, another neurocognitive and tumor predisposition disorder, an attempt has been made to capture the burden of the disease by introducing the TAND checklist, encompassing 'Tuberous sclerosis-associated neuropsychiatric disorders'. This could serve as an inspiration for such initiatives in the field of neurofibromatosis type 1 [63].

Strengths and limitations

In a qualitative observational study, the subjects that are to be discussed can be standardized, but conversations themselves cannot be standardized. Given the sample size and the nature of this study, these differences cannot be explored in a quantitative way. Future studies with larger

sample sizes and a quantitative may focus on systematic differences between age groups, genders or between parents and patients.

Using focus groups as a means to explore worries and needs has the possible drawback of participants feeling limited in their ability to express feelings or concerns in the presence of other patients or parent. In our focus groups, the atmosphere was quite open and stimulating, and almost all participants actively joined the conversation. However, problems with more intimate matters such as sexuality, addiction, suicidal thoughts, and finance were hardly reported.

All patients who participated in this study were members of the Dutch NF1 patient organization (NFVN). For this reason, our sample may be biased towards relatively well-informed patients with a higher level of education, and parents and patients may also have a more severe phenotype. The Netherlands is a high-income country in Western Europe. This should be taken into consideration when extrapolating our results and recommendations to other societies where limitations in care infrastructure, expertise, and finances may be more prevalent.

Since a large part of the participants were adults over 30 years old, their reporting about the translational period could have suffered from 'recall bias'. For some of them, this period was quite some time ago. Healthcare services probably may have changed in the past years. However, we do feel that the recommendations in this paper directly result from the information of both younger and older participants.

The apparent data saturation during analysis suggests sufficient sample size and data quality. Other strengths of the study were the large age range, the range in level of education, and reports from both patients and parents. The ICF turned out to be an appropriate method to describe patient-related problems in almost all areas of life. The universal nature of the ICF and the apparent shortcomings of Dutch health care make our findings applicable to other countries where multidisciplinary care is not routinely offered.

Acknowledgments

We would like to thank all the participants, their family members, and the Dutch patient's organization (Neurofibromatosis Vereniging Nederland) for their participation and support in this study. We are grateful to Alanna Jacobs, who helped to edit the final version of the manuscript.

References

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010;152A:327-332.

2. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999;89:1-

3. NIH nioh. Neurofibromatosis. NIH Consens Statement 1987 Jul 13-15. 1987;6:1-19.

4. Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): diagnosis and management Handb Clin Neurol 2013;115:939-955.

5. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in child with neurofibromatosis type 1. Neurology 2005;65:1037-1044.

6. Hyman SL, Arthur Shores E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disc Dev Med Child Neurol 2006;48:973-977.

7. Leschziner GD, Golding JF, Ferner RE. Sleep disturbance as part of the neurofibromatc type 1 phenotype in adults. Am J Med Genet A 2013;161A:1319-1322.

8. Morris SM, Acosta MT, Garg S, et al. Disease Burden and Symptom Structure of Autisr Neurofibromatosis Type 1: A Study of the International NF1-ASD Consortium Team (INFACT). JAMA Psychiatry 2016;73:1276-1284.

9. Constantino JN, Zhang Y, Holzhauer K, et al. Distribution and Within-Family Specificity Quantitative Autistic Traits in Patients with Neurofibromatosis Type I. J Pediatr 2015;167:621 e621.

10. Mautner VF, Granstrom S, Leark RA. Impact of ADHD in adults with neurofibromatosis 1: associated psychological and social problems. J Atten Disord 2015;19:35-43.

11. Descheemaeker MJ, Plasschaert E, Frijns JP, Legius E. Neuropsychological profile in ad with neurofibromatosis type 1 compared to a control group. J Intellect Disabil Res 2013;57:8 886.

12. Van Lierde A, Menni F, Bedeschi MF, et al. Healthcare transition in patients with rare genetic disorders with and without developmental disability: neurofibromatosis 1 and Williar Beuren syndrome. Am J Med Genet A 2013;161A:1666-1674.

13. Vranceanu AM, Merker VL, Park ER, Plotkin SR. Quality of life among children and adolescents with neurofibromatosis 1: a systematic review of the literature. J Neurooncol 2015;122:219-228.

14. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013;55:111-125.

15. Farre A, Wood V, McDonagh JE, et al. Health professionals' and managers' definitions of developmentally appropriate healthcare for young people: conceptual dimensions and embedded controversies. Arch Dis Child 2016;101:628-633.

16. Korf BR. Neurofibromatosis type 1 (NF1): Management and prognosis [online]. Available at: https://www.uptodate.com/contents/neurofibromatosis-type-1-nf1-management-and-prognosis.

17. Rauen KA, Huson SM, Burkitt-Wright E, et al. Recent developments in neurofibromatoses and RASopathies: management, diagnosis and current and future therapeutic avenues. Am J Med Genet A 2015;167A:1-10.

18. Oates EC, Payne JM, Foster SL, Clarke NF, North KN. Young Australian adults with NF1 have poor access to health care, high complication rates, and limited disease knowledge. Am J Med Genet A 2013;161A:659-666.

19. Vranceanu AM, Merker VL, Park E, Plotkin SR. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: a systematic review of the literature. J Neurooncol 2013;114:257-262.

20. Lai JS, Jensen SE, Patel ZS, Listernick R, Charrow J. Using a qualitative approach to conceptualize concerns of patients with neurofibromatosis type 1 associated plexiform neurofibromas (pNF) across the lifespan. Am J Med Genet A 2017;173:79-87.

21. Crawford HA, Barton B, Wilson MJ, et al. The Impact of Neurofibromatosis Type 1 on the Health and Wellbeing of Australian Adults. J Genet Couns 2015.

22. Barke J, Harcourt D, Coad J. 'It's like a bag of pick and mix--you don't know what you are going to get': young people's experience of neurofibromatosis Type 1. J Adv Nurs 2014;70:1594-1603.

23. Draucker CB, Nutakki K, Varni JW, Swigonski NL. The health-related quality of life of children, adolescents, and young adults with neurofibromatosis type 1 and their families: Analysis of narratives. J Spec Pediatr Nurs 2017;22.

24. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349-357.

25. European-Commission. Inclusion strategy of the "Youth in Action"programme (2007-2013) [online]. Available at: https://www.salto-youth.net/downloads/4-17-1294/InclusionStrategyYiA.pdf. Accessed 22nd July 2017.

26. van Staa A, van der Stege HA, Jedeloo S, Moll HA, Hilberink SR. Readiness to transfer to adult care of adolescents with chronic conditions: exploration of associated factors. J Adolesc Health 2011;48:295-302.

27. ATLAS.ti 6 [computer program]. Berlin: 2011.

28. Braun V CV. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3:77–101.

29. WHO WHO. International Classification of Functioning, Disability and Health (ICF) [online]. Available at: http://www.who.int/classifications/icf/en/. Accessed 22 December 2016.

30. Gilboa Y, Rosenblum S, Fattal-Valevski A, Josman N. Application of the International Classification of Functioning, Disability and Health in children with neurofibromatosis type 1: a review. Dev Med Child Neurol 2010;52:612-619.

31. UNESCO Ifs. International Standard Classification of Education; ISCED 2011. Montreal, Quebec, Canada2012.

32. Afridi SK, Leschziner GD, Ferner RE. Prevalence and clinical presentation of headache in a National Neurofibromatosis 1 Service and impact on quality of life. Am J Med Genet A 2015;167A:2282-2285.

33. Wolters PL, Burns KM, Martin S, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. Am J Med Genet A 2015;167A:2103-2113.

34. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. Dev Med Child Neurol 2005;47:237-242.

35. Cohen JS, Levy HP, Sloan J, Dariotis J, Biesecker BB. Depression Among Adults with Neurofibromatosis Type 1: Prevalence and Impact on Quality of Life. Clin Genet 2014.

36. Pasini A, Lo-Castro A, Di Carlo L, et al. Detecting anxiety symptoms in children and youths with neurofibromatosis type I. Am J Med Genet B Neuropsychiatr Genet 2012;159B:869-873.

37. Lindberg NM, Wellisch D. Anxiety and compliance among women at high risk for breast cancer. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 2001;23:298-303.

38. Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. International journal of cancer 2001;93:608-611.

39. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002;39:311-314.

40. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-563.

41. Pride NA, Crawford H, Payne JM, North KN. Social functioning in adults with neurofibromatosis type 1. Res Dev Disabil 2013;34:3393-3399.

42. Ejerskov C, Lasgaard M, Ostergaard JR. Teenagers and young adults with neurofibromatosis type 1 are more likely to experience loneliness than siblings without the illness. Acta Paediatr 2015;104:604-609.

43. Hummelvoll G, Antonsen KM. Young adults' experience of living with neurofibromatosis type 1. J Genet Couns 2013;22:188-199.

44. Crawford HA, Barton B, Wilson MJ, et al. The Impact of Neurofibromatosis Type 1 on the Health and Wellbeing of Australian Adults. J Genet Couns 2015;24:931-944.

45. Barke J, Coad J, Harcourt D. Parents' experiences of caring for a young person with neurofibromatosis type 1 (NF1): a qualitative study. Journal of community genetics 2016;7:33-39.

46. Hartley SL, Seltzer MM, Head L, Abbeduto L. Psychological Well-being in Fathers of Adolescents and Young Adults with Down Syndrome, Fragile X Syndrome, and Autism. Family relations 2012;61:327-342.

47. Briegel W, Schneider M, Schwab KO. 22q11.2 deletion syndrome: behaviour problems of children and adolescents and parental stress. Child: care, health and development 2008;34:795-800.

48. Pozo P, Sarria E. Still stressed but feeling better: Well-being in autism spectrum disorder families as children become adults. Autism 2015;19:805-813.

49. Esposito M, Marotta R, Roccella M, et al. Pediatric neurofibromatosis 1 and parental stress: a multicenter study. Neuropsychiatr Dis Treat 2014;10:141-146.

50. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. Pediatrics 2005;115:112-120.

51. Bindels-de Heus KG, van Staa A, van Vliet I, Ewals FV, Hilberink SR. Transferring young people with profound intellectual and multiple disabilities from pediatric to adult medical care: parents' experiences and recommendations. Intellect Dev Disabil 2013;51:176-189.

52. Fegran L, Hall EO, Uhrenfeldt L, Aagaard H, Ludvigsen MS. Adolescents' and young adults' transition experiences when transferring from paediatric to adult care: a qualitative metasynthesis. Int J Nurs Stud 2014;51:123-135.

53. Lotstein DS, Ghandour R, Cash A, McGuire E, Strickland B, Newacheck P. Planning for health care transitions: results from the 2005-2006 National Survey of Children With Special Health Care Needs. Pediatrics 2009;123:e145-152.

54. NICE. Transition from children's to adults' services. In: Excellence NIfHaC, ed.2016.

55. Schor EL. Transition: changing old habits. Pediatrics 2015;135:958-960.

56. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81-88.

57. Mautner VF, Granstrom S, Leark RA. Impact of ADHD in Adults With Neurofibromatosis Type 1: Associated Psychological and Social Problems. J Atten Disord 2012.

58. WHO Who. Mental health: strengthening our response [online]. Available at: http://www.who.int/mediacentre/factsheets/fs220/en/. Accessed October 21, 2016.

59. Riccardi VM. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. 2nd ed. Baltimore, MD: Johns Hopkins University Press, 1992.

60. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421-1425.

61. Upadhyaya MaC, D.N. Neurofibromatosis Type 1. Berlin Heidelberg: Springer-Verlag, 2012.

62. van der Vaart T, Plasschaert E, Rietman AB, et al. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. Lancet Neurol 2013;12:1076-1083.

63. de Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. Pediatr Neurol 2015;52:25-35.

CHAPTER 9.

General discussion

Neurofibromatosis type 1 (NF1) is a neurogenetic disorder with a highly variable behavioral phenotype. Compared to former research, the main contribution of this thesis to the behavioral phenotype of NF1 is due to larger sample sizes, broader outcome measures, the longitudinal design, or the associations between phenotype and quality of life and participation. In this chapter, overarching conclusions will be drawn regarding all studies described in Chapters 2 to 8. In addition to the conclusions already drawn in previous chapters, clinical implications, recommendations for assessment and treatment of individuals with NF1, and suggestions for future research are formulated. This information is underlined in the text below.

Behavioral phenotype of NF1

Chapters 2 to 5 focus on clarifying the behavioral phenotype of NF1 on the different levels of the ICF. Motor, emotional, and behavioral problems in children and adolescents are common in NF1, probably even more than was thought before.

Motor problems in children with NF1

We found that almost half of the children of 4 to 16 years with NF1 have severe motor problems, independent from age or intelligence. In the general population, this is about 5-6% of school-aged children.[1] The prevalence of severe motor problems is comparable to or even larger than the prevalence of ADHD in NF1.[2-4] In addition, ADHD, ASD, and externalizing problem behaviors are often associated with motor problems in NF1.[5] Compared to former studies, our study used a larger group of children and a broader test-battery: the Movement-ABC[6, 7], which is regarded as an important part of the assessment needed for diagnosing developmental motor problems in children.[8]

Although the DSM-5[9], the psychiatric classification system for mental disorders, started as a descriptive system, in some classifications there are causal elements referring to the cause of a disorder. In the description of *developmental coordination disorder (DCD)*, one of the criteria states: “the motor skills deficits are not attributable to a neurologic condition affecting movement (e.g., cerebral palsy, muscular dystrophy, degenerative disorder)”. The question is how ‘neurologic conditions’ are defined and whether NF1 needs to be regarded as such. Since NF1 can affect bones, muscles, and other structures of the musculoskeletal system, this needs to be addressed first in clinical assessment. Despite the high prevalence, DCD is probably underrecognized by health care professionals.[1] Many of these motor difficulties continue into adulthood and

evidence-based interventions for children with DCD are known and often available.[10] Not diagnosing DCD could impede referral to the providers of these interventions, which may have a negative effect on the well-being and participation of individuals with NF1. When developmental motor problems are this severe, the professionals who have expertise in motor development (i.e. rehabilitation doctors, physiotherapists, pediatricians, neurologists, psychiatrists, or healthcare psychologists), may consider diagnosing DCD in NF1.

Children with NF1 can have decreased mineral density, bone strength, and muscle mass,[11] and may have reduced muscle force.[12] Future longitudinal and treatment studies may clarify to what extent these symptoms contribute to the development of motor problems in NF1. This could also provide an answer to questions regarding the *musculoskeletal or neurodevelopmental* origin of motor problems in NF1.

Emotional and behavioral problems in NF1

Chapter 3 describes the increase of internalizing behavioral problems (also: 'emotional problems') in children between 4 and 8 years of age. Interestingly, no association was found between these *emotional problems and intelligence or language development*. This lack of association was also found in Chapter 7, describing a factor analysis resulting in one component with cognitive outcome measures and a relatively independent second component with emotional and behavioral problems and psychosocial quality of life. Since the correlation between cognition and quality of life appear to be low according to these studies, it can be disputed whether cognitive problems in children with NF1 should be a priority in treatment. Possibly the educational system in the Netherlands and Belgium (Flanders) provides the opportunity to adapt education to fit the capacities of children. In general, quality of life is higher in people with higher educational levels. They are less often unemployed, better paid, have better homes and a better appreciation of their own health. People with a lower level of education are more vulnerable in times of economic downturn.[13] Since both cognition and behavior are important features of the behavioral phenotype of NF1, psychological assessment should include both aspects.

Another relationship that emerges in different studies in this thesis is *the association between physical and behavioral aspects* of NF1. The severity of NF 1 in adults as defined by the Riccardi scale,[14] appears to be associated with quality of life in some studies.[15] Using a self-constructed scale for severity and a measure for total tumor burden, Martin et al.[16] found an association between severity and social-emotional outcomes. We did find an association between

emotional and behavioral problems and quality of life but not with NF1 severity. Different definitions of severity and different behavioral outcome measures may be the reason for the differences between these findings. There is a wide variety of NF1 symptoms that can contribute to the perceived severity of NF1. For this reason, it is debatable whether a single scale or rating can reflect this diversity when it reduces severity to a limited classification in four levels or when it defines severity as the sum of a number of symptoms. Somatic symptoms include tumor burden, malignancy, neurological symptoms, musculoskeletal symptoms, dermatological symptoms, and more. In addition, cognitive, emotional, social, and behavioral symptoms known to affect quality of life and participation must be assessed in order to get a complete impression of the severity of NF1. It would be better not to add or combine these somatic, cognitive, emotional, social, and behavioral symptoms in future research, but to consider them as separate predictors of quality of life and participation.

Having a parent with NF1 can also be a factor that influences outcome in children with NF1. Comparing children with a *familial mutation* to children with a sporadic mutation, the study in Chapter 3 did not find a difference in intelligence or behavioral problems but children with a familial mutation seemed to score lower on all language tests at kindergarten age. Future research may explore genetic or sociocultural transmission as explanations of language problems in young children with familial NF1. Interestingly, having a parent with NF1 can possibly be a beneficial factor, since more children with familial mutations return for follow-up at a later age in this longitudinal study.

In all three studies from chapters 3 to 5, the emphasis on *internalizing behavioral problems* in NF1 in children, adolescents, and young adults is clear. The only average scores (on a group level) in a broad screening of emotional and behavioral problems are the scores on scales for externalizing and in particular aggressive behavior. The internalizing domain, also called the domain of emotional rather than behavioral problems, includes anxiety, depression, social withdrawal, and somatic complaints. Although scores for somatic symptoms in NF1 are showing the largest deviation from the scores of children in the normative population, also anxious, depressed and withdrawn behavior is clearly present in NF1. These behaviors may remain unnoticed at home, at school, or at work for a long time, risking more severe psychopathology.[17-19] Early recognition of anxiety and depression and easy access to mental health care is necessary to prevent lower quality of life and late or even too late treatment of these serious disorders.

Attention problems and social problems are probably the most prevalent and most serious neurobehavioral problem in NF1. In the study described in chapter 3, 33% of the children had an ADHD diagnosis and in a recent study from our ENCORE group, about 11% have an autism spectrum disorder.[20] This problem is even greater in NF1 than these percentages can express, since they only refer to children and adolescents with problems in the clinical range, whereas a larger group has problems in the borderline of subclinical range. Attentional and social problems should be a focus of attention in the follow-up of NF1 since these problems interact and can reinforce each other.[21, 22] Children with one or two of these problems are at risk of learning problems, social isolation, and other comorbid psychopathology. Early and regular screening and intervention into adulthood can reduce the risk of these consequences.

Quality of life and participation in daily life

Chapter 5 and 8 illustrate determinants of quality of life and the worries of adults about their daily activities and participation. Adolescents and young adults with NF1 have lower mental and physical quality of life (QoL) and important determinants were sex, fatigue, and internalizing and social problems. Until now, fatigue was not a recurring topic in NF1 research. In clinical practice, however, fatigue is very often an important point of concern in consultations of adolescents and adults with NF1. Now that we *know fatigue is such a strong determinant of quality of daily life*, this needs to be reflected in assessments, care, outcome measures, and research in the near future. In a consultation of adult patients with NF1 in the Netherlands during the drafting of the Dutch standard for NF1 care, chronic fatigue was the second most prevalent complaint, after cutaneous neurofibroma. People with NF1 often complain about reduced physical and mental resilience. The recently developed INF1-QOL-Questionnaire[23] could be extended with the question:

'Does fatigue interfere with studying, work, daily living activities or social activities? (e.g. increased concentration problems due to fatigue, not being able to attend a full day at school or work, not being able to have a family life or social life due to fatigue).'	
No problems due to fatigue	□0
Mild problems due to fatigue but able to perform activities	□1
Moderate problems due to fatigue cause me some difficulty in performing activities	□2
Severe problems due to fatigue stop my activities	□3

In literature and standards of care, fatigue is being associated with stress, sleeping problems, headache, attention/concentration problems, pain, scoliosis, pulmonary (valve) stenosis, (brain) tumors, and depressed mood. At present, it is unclear which of these problems play a part in causing or increasing fatigue and which of these complaints are consequences of fatigue. Future research needs to focus on the emergence of fatigue in the natural history of NF1 and on the position of fatigue within this field of complaints. Whether severe fatigue symptoms or their predictors also occur in children may be answered in such studies. Next to this, current successful methods aiming at symptomatic treatment of chronic fatigue[24] may well be effective in NF1 in the same way that medication effective in the symptomatic treatment of ADHD is also effective in treating ADHD-symptoms in NF1.[3]

In our qualitative study, focusing on worries and care needs (Chapter 8), it again became apparent that adults with neurofibromatosis type 1 and their parents need a broad scope of care and support from their care providers. Comparing this study with a comparable study we conducted in adults with TSC and their parents, [25] patients with NF1 experience a lack of routine assessment of mental health issues. In TSC, the Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) [26] – screening already addresses this need in the TSC-population. A '*Neurofibromatosis 1 – associated neuropsychiatric disorders*'- screening tool could assist NF1 patients and professionals, especially those working outside NF1 centers for expertise, to also focus on this important part of NF1 care. A concept version of an adaptation and extension of the TAND into a 'NAND', can be found as an appendix at the end of this chapter.

Both patients with NF1 and TSC indicate they need to focus not only on complaints about somatic or mental health problems but also on daily activities and participation. The ICF model is a

useful framework to also incorporate socioeconomic, personal, and environmental issues in a broad assessment of the needs of people with NF1 and their families. Future initiatives to develop these 'patient-reported outcome measures' (so-called PROM's) may be supported by the USA National Institutes of Health (NIH), which started the PROMIS initiative, that currently also comprises local initiatives such as the Dutch-Flemish PROMIS group.[27] This also fits well with the current tendency to focus on 'Value-based healthcare' (VBHC) aiming to improve 'patient value' via patient outcomes and cost-effectiveness.

Also in other neurobehavioral syndromes such as TSC,[25] Angelman syndrome, and Fragile X syndrome,[28] there is a growing interest in *daily living challenges and family impact* of these syndromes, also to find whether and how presently available as well as future treatment options can impact on the lives of these individuals. Outcomes of qualitative studies are useful raw material for constructing syndrome-specific instruments with known psychometric properties. With these instruments, larger groups of patients and their families from various countries and cultures can be asked to contribute to the knowledge of associations between a behavioral phenotype, quality of life, and participation in daily life.

Due to the large variation in domains that are affected by NF1, the care for people with NF1 is per definition a *team effort.* Clinical geneticists, neurologists, pediatricians, dermatologists, ophthalmologists, and surgeons each contribute to a part of the somatic care. In the Dutch standard of care,[29] next to the contribution of somatic specialists, also the contribution of parents, teachers, psychologists, psychiatrists, physical therapists, occupational therapists, speech/language therapists, nurses, and social workers is described. In addition to cooperation between all these specialists, a well-organized, government-supported patients' association is an important, low-threshold means to inform patients, parents, and other professionals, and to facilitate the exchange of experiences and ideas.

Strengths & weaknesses

The NF1 outpatient clinic in Rotterdam has been active for almost 35 years. In a growing number of countries, systematic follow-up of NF1 is organized. In these years, the knowledge about NF1 and the experience in care and research is growing, together with the amount of data collected on genetic, somatic, cognitive, and behavioral factors in people with NF1. This facilitates research into NF1 with a growing number of patients, a longitudinal perspective, and increasing data quality. A major effect on research of this growing population in follow-up is the large number of patients

that now can be included in cross-sectional studies and be prepared for future trials, contributing to the 'trial readiness' of our expertise center. If the care that the center provides is valued by patients and parents, people return for re-evaluation after a predetermined period of time. This enables data collection on the natural history of NF1 and the study of the acquisition of skills and the emergence of problems in longitudinal research. At this moment, longitudinal studies in NF1 are scarce and also the study described in Chapter 3 suffered from a small sample size. There is a need for future research in larger populations to confirm or differentiate the findings of underpowered studies.

Recruitment of patients for trials is easier with more than 500 patients in active care. However, NF1 is a rare disease and the number of participants necessary for sufficient power can still be more than a national reference center can provide. For this reason, an international collaboration of national or regional reference centers is crucial, as was also the case during the recruitment of participants for the SIMCODA study. Partly for this reason, ENCORE participates in the European reference network (ERN) GENTURIS for patients with one of the rare genetic tumor risk syndromes (www.genturis.eu).

A drawback of performing research in an academic, tertiary hospital is the risk of 'academic bias': since mainly the people with more serious complaints may visit national reference centers. Trials evaluating the treatment of NF1-related symptoms may suffer from a bias towards the more severely affected individuals. On the other hand, particularly the more severely affected patients have the greatest need for this type of specialized care and for the results of future therapeutic research. The current development of regional treatment centers in the Netherlands in addition to one central expertise center could make care more accessible to all patients and may reduce this bias.

Longitudinal studies and trials in NF1

Both longitudinal studies and trials are costly projects requiring funding for care and research and time from patients, families, care providers, and researchers. This requires a thorough consideration of criteria for the selection of outcome measures in advance. The information that is collected in follow-up needs to contribute to the knowledge about the individuals with a neurogenetic disorder and their families. Next to this, it can also give valuable information about the disorder in general. At a micro-level, this information needs to enable the healthcare

professional to answer questions from his or her clients about their daily lives. At a macro-level, it may help to answer questions regarding the behavioral phenotype.

Selection of outcome measures

Most criteria for the quality of psychological outcome measures are widely accepted. A commission of the Dutch Institute for Psychology (NIP) formulated these criteria in the COTAN guidelines (*Commissie Testaangelegenheden Nederland*: Commission of Assessment Issues in the Netherlands). This commission evaluates all submitted instruments using criteria for principles of test construction, norms, reliability, content validity, and criterion validity. Although knowledge about these criteria is part of the general training of most psychologists, a critical evaluation by an expert team is a valuable additional tool for the practicing psychologist. However, not all instruments are evaluated by COTAN and evaluation of outcome measures by the psychologist who is available for the project will be necessary on many occasions. This is all the more necessary when it comes to the usefulness of instruments for a specific target group, such as NF1.

International initiatives to aid in the selection of outcome measures are the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative[30] and the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[31] In 2016, this led to the development of a guideline for selecting outcome measurement instruments.[32]

Outcome measures in follow-up

A structured follow-up administering preset instruments at preset ages could facilitate a longitudinal view on the natural history of the disorder. The VOLG project (Dutch acronym for 'Early recognition of problems in learning and behavior'), as described in the Introduction of this thesis, is such a follow-up program. The VOLG follow-up is conducted at our center of expertise and at several NF1 treatment centers in the Netherlands and is offered to all children and adolescents. A major concern for the VOLG program, which also aims at good data integrity, is whether children return to follow-up, years after their first assessment. Referral by a physician specialized in NF1 may contribute to long-term compliance. Apart from this, psychologists need to listen and respond to the concerns of parents, and they need to provide a thorough evaluation in this assessment and state useful recommendations for parents and children.

Recommendations regarding the instruments a thorough evaluation should consist of:

- associated with NF1-related deficits
- good psychometric properties (e.g. recent, national norms, test-retest, and interrater reliability, construct validity)
- measure a construct over a long period of time to facilitate long-term comparisons and longitudinal research
- internationally used in NF1-research to facilitate comparison in research or comparison with other NF1 populations
- sensitive for changes in time or changes caused by the intervention

Following the present knowledge about the behavioral phenotype of NF1, Table 1 provides an overview of the core constructs and (as an example) instruments that are frequently used in the field of NF1 research.

Table 1. Core constructs and corresponding instruments in Neuropsychological assessment of individuals with NF1

Core construct	Examples of frequently used instruments		
Age	Preschool	School-age	Adult
		Cognition	
Intelligence	Bayley scales of infant development	Wechsler scales	Wechsler scales
Speech	Assessment by speech/language therapist		
Language	CELF-preschool	CELF	*
Visuospatial/visuoconstructive	VMI	VMI, Rey CFT	VMI, Rey CFT
Executive functions	Nepsy *BRIEF-P*	Nepsy/D-KEFS/BADS-C *BRIEF*	D-KEFS/BADS *BRIEF-A*
Attention	Nepsy	Nepsy	CPT
Motor performance	Movement-ABC,[6] *DCD-Q, M-ABC checklist*	Movement-ABC, *DCD-Q, M-ABC checklist*	*
		Emotional, behavioral and social functioning	
Emotional and behavioral problems- general screening	CBCL/TRF SDQ	CBCL/TRF/YSR SDQ	ABCL/ASR
ADHD-screening	DSM criteria-based questionnaire and interview (Conners)[33]	DSM criteria-based questionnaire and interview (Conners)[33]	DSM criteria-based questionnaire and interview (DIVA)[34]
ASD-screening	ADOS; *SRS*	ADOS; *SRS*	ADOS; *SRS*
Anxiety/depression	*SCARED*	*SCARED/CDI*	*SCAARED/BDI*
Social cognition/functioning	SRS	SRS	SRS
Fatigue	*PedsQL- Fatigue*	*PedsQL- Fatigue/CIS*	*CIS*
		Daily life	
Quality of life	*ITQOL*	*CHQ*	*SF-36*
Sleep	*SDSC*	*SDSC*	*ESS/PSQI*
Academic performance	Standardized assessment of reading, spelling, reading comprehension, and arithmetic		
Participation	*M-FUN-PS*	*CAPE*	*IPA*

Italics: proxy- and self-rating scales *only assess when necessary to answer referral question

Abbreviations of tests:

BADS (-C): Behavioural Assessment of the Dysexecutive Syndrome (in Children)

BDI: Beck Depression Inventory

BRIEF (-P/-A): Behavior Rating Inventory Executive Functions (-Preschool/-Adult Self-rating)

CAPE: The Children's Assessment of Participation and Enjoyment

CBCL/ABCL: Child/Adult Behavior Checklist; TRF: Teacher's Report Form; YSR/ASR: YSR, youth self-report.

CDI: Children's Depression Inventory

CELF: Clinical Evaluation of Language Fundamentals

CHQ: Child Health Questionnaire

CIS: Checklist Individual Strength

CPT: Continuous Performance Test

DCD-Q: Developmental Coordination Disorder- Questionnaire

DIVA: Diagnostic Interview for ADHD in adults

D-KEFS: Delis–Kaplan Executive Function System

ESS: Epworth sleepiness scale

IPA: Impact on Participation and Autonomy

ITQOL: Infant Toddler Quality of life

M-FUN-PS: Miller Function & Participation Scales

Movement-ABC: Movement Assessment Battery for Children

Nepsy: Neuropsychological testing battery for children

PedsQL- Fatigue: Pediatric Quality of Life Inventory- Fatigue module

PSQI: Pittsburgh sleep quality index

Rey CFT: Rey's Complex Figure test

SCAARED: Screen for Adult Anxiety Related Disorders

SCARED: Screen for Child Anxiety Related Emotional Disorders

SDSC: Sleep Disturbance Scale for Children questionnaire

SDQ: Strengths and Difficulties Questionnaire

SF-36: Short form Health Survey with 36 questions

SRS: Social responsiveness scales

VMI: Developmental Test of Visual-Motor Integration

Outcome measures in trials

Trials require large efforts from patients, parents, and professionals and funding from clinical institutions, funding organizations, and society before they can inform us about the effectivity of the target intervention. For this reason, ample time needs to be paid to the process of selecting outcome measures. Chapters 5, 6, and 7 are all associated with trials aiming at treating NF1. Chapter 5 describes the starting point of a trial focusing mainly on psychosocial complaints. Like many other studies, this 'SPOT trial' addresses the symptomatic treatment of the effects of NF1. In the near future, the results of this SPOT study and the effects of a psychosocial intervention on mental quality of life will be published.

In the last twenty years translational research has added a more causal approach to treatment. The cooperation of fundamental research with clinical research facilitated translating preclinical trials into clinical trials targeting cognitive and behavioral problems. This type of research has only just started and more trials are running at this very moment (e.g. the EXCEL trial to evaluate the effect of lamotrigine on cognition and behavior in NF1; EudraCT Number: 2013-003405-26). During and after these trials, lessons are learned every day from current trials to contribute to better future trials. One of these lessons concerns the selection of outcome measures. Critical evaluation of the outcome measures can make a valuable contribution to the interpretation of current trials and the selection of outcomes in future trials. Chapter 7 illustrates how running or past trials can provide information about the value of generally used instruments. Evaluation of the outcome measures themselves and the relationship between these measures provides useful information for future trials. This paper itself kindled a discussion in the field of NF1 trials as to the selection of broad outcome measures (i.e. quality of life surveys or intelligence test batteries) or specific outcome measures (i.e. more explanatory outcomes tapping specific neuropsychological functions). Walsh et al. argued that researchers should select hypothesis-driven domains for a trial. We responded that a clinically relevant outcome measure is needed when deciding whether a certain treatment should be given to children with learning difficulties.[35] The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration aims to reach a consensus on clinical trials endpoints in NF1 research. Future initiatives should focus first on accumulating and integrating knowledge about outcome measures to finally harmonize the selection of neuropsychological outcome measures in NF1.

Conclusion

Behavioral phenotyping in NF1 has shown to be a powerful approach to understanding the nat history of a syndrome and its frequently associated co-morbid problems. Also, NF1 is a commo neurocognitive disorder that can serve as a model for many other monogenetic syndromes. Th thesis not only extends the knowledge about the phenotype but also provides guidance for the diagnosis and treatment of children, adolescents, and adults with NF1.

References

1. Blank R, Smits-Engelsman B, Polatajko H, Wilson P, European Academy for Childhood D. European Academy for Childhood Disability (EACD): recommendations on the definition, diagn and intervention of developmental coordination disorder (long version). Dev Med Child Neurol 2012;54:54-93.

2. Hofman KJ, Harris EL, Bryan RN, Denckla MB. Neurofibromatosis type 1: the cognitive phenotype. J Pediatr 1994;124:S1-8.

3. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis ty 1. Dev Med Child Neurol 2002;44:164-170.

4. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attent in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. Child Neuropsychol 2011;17:313-329.

5. Rietman AB, Oostenbrink R, Bongers S, et al. Motor problems in children with neurofibromatosis type 1. J Neurodev Disord 2017;9:19.

6. Henderson S SD, Barnett A. Movement assessment battery for children-2 second editio [Movement ABC-2]. London: The Psychological Corporation, 2007.

7. Henderson SE SD. Movement assessment battery for children manual. London: The Psychological Corporation Ltd., 1992.

8. Stuurgroep D-. Dutch Consensus statement DCD. Coördinatieontwikkelingsstoornis (Developmental Coordination Disorder) als specifiek leerprobleem. 2011.

9. [APP] APA. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA American Psychiatric Association, 2000.

10. Harris SR, Mickelson EC, Zwicker JG. Diagnosis and management of developmental coordination disorder. CMAJ 2015;187:659-665.

11. Stevenson DA, Murray M, Viskochil DH, Carey JC, Moyer-Mileur LJ. Bone mineral densit children with neurofibromatosis type 1. J Pediatr Orthop 2008;28:791; author reply 791-792.

12. Souza JF, Passos RL, Guedes AC, Rezende NA, Rodrigues LO. Muscular force is reduced i neurofibromatosis type 1. J Musculoskelet Neuronal Interact 2009;9:15-17.

13. Centraal Bureau voor de Statistiek C. Kwaliteit van leven in Nederland. Den Haag: Autho 2015.

14. Riccardi VM, Kleiner B. Neurofibromatosis: a neoplastic birth defect with two age peaks severe problems. Birth Defects Orig Artic Ser 1977;13:131-138.

15. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol 2001;137:1421-1425.

16. Martin S, Wolters P, Baldwin A, et al. Social-emotional functioning of children and adolescents with neurofibromatosis type 1 and plexiform neurofibromas: relationships with cognitive, disease, and environmental variables. J Pediatr Psychol 2012;37:713-724.

17. Chavira DA, Stein MB, Bailey K, Stein MT. Child anxiety in primary care: prevalent but untreated. Depress Anxiety 2004;20:155-164.

18. Clark MS, Jansen KL, Cloy JA. Treatment of childhood and adolescent depression. Am Fam Physician 2012;86:442-448.

19. Sigalas PD, Barkla X, McArdle P. Underdiagnosis of depression in young people. BMJ 2014;348:g170.

20. Eijk S, Mous SE, Dieleman GC, et al. Autism Spectrum Disorder in an Unselected Cohort of Children with Neurofibromatosis Type 1 (NF1). J Autism Dev Disord 2018;48:2278-2285.

21. Barton B, North K. Social skills of children with neurofibromatosis type 1. Dev Med Child Neurol 2004;46:553-563.

22. Walsh KS, Velez JI, Kardel PG, et al. Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1. Dev Med Child Neurol 2013;55:131-138.

23. Ferner RE, Thomas M, Mercer G, et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality Of Life (INF1-QOL) questionnaire. Health Qual Life Outcomes 2017;15:34.

24. Castro-Marrero J, Saez-Francas N, Santillo D, Alegre J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome. Br J Pharmacol 2017;174:345-369.

25. Both P, Ten Holt L, Mous S, et al. Tuberous sclerosis complex: Concerns and needs of patients and parents from the transitional period to adulthood. Epilepsy Behav 2018;83:13-21.

26. de Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. Pediatr Neurol 2015;52:25-35.

27. group D-FP. Dutch-Flemish PROMIS group (Patient Reported Outcomes Measurement Information System) [online]. Available at: http://www.dutchflemishpromis.nl/. Accessed March 9.

28. Dixon Weber J. SE, Berry-Kravis E., Cadavid D., Hessl D. and Erickson C. Voice of People with Fragile X Syndrome and Their Families: Reports from a Survey on Treatment Priorities. Brain sciences 2019;9.

29. NFVN NVN. Zorgstandaard Neurofibromatose type 1. Den Haag, the Netherlands: Neurofibromatose Vereniging Nederland, 2015.

30. COSMIN. Consensus-based Standards for the selection of health Measurement INstruments. [online]. Available at: http://www.cosmin.nl/. Accessed March 9.

31. COMET. Core Outcome Measures in Effectiveness Trials [online]. Available at: http://www.comet-initiative.org/. Accessed March 9.

32. Prinsen CAC VS, Rose MR, Boers M, Tugwell P, Clarke M, Williamson PR, Terwee CB. Guideline for selecting outcome measurement instruments for outcomes included in a Core Outcome Set2016.

33. Chang LY, Wang MY, Tsai PS. Diagnostic Accuracy of Rating Scales for Attention-Deficit/Hyperactivity Disorder: A Meta-analysis. Pediatrics 2016;137:e20152749.

34. Kooij JJS F, MH, . DIVA 2.0 Diagnostic Interview for ADHD in adults [online]. Available at: http://www.divacenter.eu/Content/VertalingPDFs/DIVA_2_EN_FORM%20-%20invulbaar.pdf. Accessed 16-02-2019.

35. Walsh KS, Janusz J, Wolters PL, Moll HA, van der Vaart T, Rietman AB. Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:1849-1850.

APPENDIX TO DISCUSSION

CONCEPT

NAND- Checklist (Neurofibromatosis type 1-Associated-Neuropsychiatric-Disorders)

1. Developmental milestones
    a. First smiled
    b. Sat without support
    c. Walked without holding on
    d. Used single words other than mama/dada
    e. Used two words/short phrases
    f. Toilet trained during the day
    g. Toilet trained at night

2. Current level of functioning
    a. Language
    b. Self-care
    c. Mobility
    d. Speech
    e. Ability to attend school/work

3. Behavioral concerns
    a. Anxiety
    b. Depressed mood
    c. *Withdrawn*/Extreme shyness
    d. Mood swings
    e. Aggression
    f. Temper tantrums
    g. Self-injury
    h. Absent or delayed onset of language to communicate
    i. Repeating words and phrases over and over again

j. Poor eye contact
k. Difficulties getting on with people of the same age
l. Repetitive *and ritualistic* behaviors
m. Rigidity/inflexibility
n. Overactivity/hyperactivity
o. Difficulty paying attention or concentrating
p. Restlessness/fidgetiness
q. Impulsivity
r. Difficulties with eating
s. Difficulties with fine motor skills
t. Difficulties with gross motor skills
u. Feelings of loneliness
v. Substance abuse (alcohol, tobacco, other)

4. Sleep difficulties and fatigue
a. Insomnia: difficulty falling asleep
b. Insomnia: difficulty staying asleep
c. Sleep apnea
d. Restless legs syndrome
e. Extremely tired after normal effort

5. Psychiatric disorders diagnosed

a. Attention deficit and hyperactivity disorders
b. Autism spectrum disorders
c. Anxiety disorders (panic attacks, phobias, obsessive-compulsive disorder)
d. Depressive disorders
e. Obsessive-compulsive disorders
f. Psychotic disorders (incl. schizophrenia, hallucinations and/or delusions)
g. Developmental coordination disorder
h. Eating disorders
i. Dementia and other cognitive regression

6. Intellectual ability
   a. *Conceptual skills (intellectual functioning, language, academic)*
   b. *Practical skills (Adaptive behaviors such as daily living skills, communication, personal independence, school or work functioning)*
   c. *Social skills (interpersonal skills, friendships)*

7. Academic skills- difficulties in:
   a. Reading
   b. Writing
   c. Spelling
   d. Mathematics/*arithmetic*
   e. *Reading comprehension*

8. Neuropsychological skills- difficulties in:
   a. Executive functions:
      i. *Inhibition*
      ii. Planning
      iii. Organizing
      iv. *Flexibility/ shifting attention*/dual tasking/multitasking
      v. *Working memory*
   b. Attentional skills
      i. *Focusing attention*
      ii. *Sustaining attention*
      iii. *Dividing attention*
   c. *Language skills:*
      i. *Language comprehension(receptive language)*
      ii. *Language expression (expressive language)*
   d. Memory skills (recognition and recall)
   e. Visuospatial skills (navigation, drawing, constructing)
   f. Disorientation *(time, place, person)*

9. Psychosocial functioning
    a. Self-esteem
    b. High levels of stress
    c. High levels of stress of parents
    d. Family functioning
    e. Relationship difficulties

10. Impact of NAND: Taken these difficulties together, how much have these bothered, troubled, or distressed you/your child/your family? (Scale from 0-Not at all to 10-Extremely)

11. Prioritizing: top priorities to work on next

12. Additional concerns

13. Strengths and protective factors

14. Health-care professional rating of the impact of NAND
    (Scale from 0-Not at all to 10- Extremely)

15. *Current medication*

Questions 3 to 9 end with:

- Evaluation, support or treatment in the past
- Wishing further evaluation, support or treatment

Cursive: NF1- related changes and additions to the TAND

This list is an adaptation of the TAND:

de Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis-associated neuropsychiatric disorders (TAND) and the TAND Checklist. Pediatr Neurol 2015;52:25-35.

Rietman AB, 2019

Appendices

I. Summary
II. Samenvatting (Dutch Summary)
III. Abbreviations
IV. Co-authors and affiliations
V. List of Publications
VI. PhD Portfolio
VII. Dankwoord
VIII. Curriculum vitae

I. Summary

Neurofibromatosis type 1 (NF1) is a genetic disorder or syndrome caused by changes in the *NF1* gene on chromosome 17q11.2. NF1 occurs in 1:2,000 to 4,000 people, of whom about half are 'new mutations' meaning parents do not have NF1. NF1 leads to symptoms in the appearance of people, such as light brown spots on the skin (so-called *café-au-lait* macules), lumps on or in the skin but also to an increased risk of having benign and malignant tumors. There is a 7-13% lifetime risk of developing malignant peripheral nervesheath tumors. Most symptoms occur in the nervous system, the skin, and the bones. This leads to unpredictable and variable complications. In adults, sex and age do not seem to be associated with NF1 severity, but there appears to be an association with general quality of life. Although the diagnostic criteria are largely somatic and the physical symptoms are serious and impressive, cognitive deficits and behavioral problems are the most common complications of NF1 in children.

Genotype is the genetic makeup or code of cells or of an organism. The genotype, together with other genetic and environmental factors determines one's phenotype. The *phenotype* of an organism is the combination of characteristics, including the physical appearance and properties, development, and behavior. A *behavioral phenotype* includes cognitive, personality, and behavioral patterns. Some behavioral phenotypes may be psychiatric disorders or syndromes. Neurocognitive and psychosocial assessments can provide a profile of strengths and weaknesses, a behavioral phenotype of the cognitive, sensory, motor, educational, behavioral, social, and emotional characteristics of people with NF1.

Behavioral phenotype of NF1

The average full-scale intelligence quotient (IQ) of children with NF1 is about 10 to 15 points lower than the IQ in the general population and also compared to siblings without NF1. Intellectual disability is twice as common in NF1 and there are more individuals with NF1 who have an IQ below 70. Other cognitive problems in NF1 are associated with speech and language, visuospatial skills, executive functions (inhibition, planning, and flexibility), attention, and motor performance. The majority of the behavioral problems found in NF1 are emotional problems such as anxiety, depression, and social withdrawal. The most common behavioral disorder in NF1 is ADHD (attention-deficit/hyperactivity disorder): ADHD occurs in 30 to 50% of the children with NF1 (compared to 5% of children in the general population). They also have poorer social skills and there is an increased risk of autism spectrum disorders (ASD).

Effects of NF1 in daily life consist of sleeping problems, learning problems, and a need for additional support and treatment. Both the people with NF1 themselves and their parents and families experience higher levels of stress, also due to difficulty coping with the uncertainty about the course of NF1. Health-related quality of life (QoL) is lower in children and parents, particularly when bodily pain is involved.

This thesis aims to contribute to the knowledge about NF1 on cognitive, behavioral, emotional, and social domains of the behavioral phenotype and the effects of this phenotype on daily life. By improving assessment and treatment, the care for and the quality of life of individuals with NF1 can be improved. The first five chapters deal with motor, emotional, behavioral, and cognitive problems, fatigue, and participation. Following, this knowledge is applied in three studies, the SPOT study, the SIMCODA study, and a qualitative study into worries and care needs.

Chapter 2 focuses on motor problems of children with NF1 and possible predictors. This study uses a broad motor performance test battery with a relatively large group of children with NF1. Sixty-nine children with NF1, aged 4 to 16 years had a motor, psychological, and neurological evaluation. Motor performance was measured with the M-ABC: Movement Assessment Battery for Children. Sixty-one percent of these children scored within the clinical range of the M-ABC. In analyses, motor problems were associated with ADHD, ASD, and externalizing behavioral problems (rule-breaking behavior and aggression). Motor outcome was not predicted by age, intelligence, scoliosis, hypotonia, nor hypermobility. The study concludes that motor problems are among the most common comorbid developmental problems in children with NF1, and these problems do not diminish with age. Because of their impact on daily functioning, motor problems need to be specifically addressed in diagnosis, follow-up, and treatment of NF1.

Chapter 3 is a longitudinal study about the development of emotional and behavioral problems in young children with NF1 in association with their intellectual and language development. At the first assessment at preschool age, we evaluated language skills, intelligence, and emotional and behavioral problems as reported by parents. The second assessment at school-age evaluated intelligence, and emotional and behavioral problems as reported by parents and teachers. Of the 61 children (mean age 4½ years) with NF1 who had a first assessment, 38 children had a second assessment after 3½ years (mean age 8 years). Parent-rated internalizing behavioral problems (anxious, withdrawn, and depressed behavior and/or somatic complaints) significantly increased with age in this group. Intelligence and language development were not associated with these

internalizing problems. The study concludes that internalizing problems at pre-school age may be predictive of internalizing problems at school age.

Chapter 4 is a study describing the emotional and behavioral problems of a large group of children and adolescents with NF1. Parents of 183 children and adolescents with an average age of 11 years (range 6-17) completed the Child Behavior Checklist (CBCL). In addition, 173 teachers completed the Teacher's Report Form (TRF) and 88 adolescents (children from 11 to 17 years) completed the Youth Self-Report (YSR). According to parents, 32% had behavioral and emotional problems (compared to 10% in the general population). This percentage was much lower when rated by teachers or adolescents themselves. The most striking scores from all informants were on scales for Somatic complaints, Social problems, and Attention problems. Attention problems were associated with lower verbal IQ, male gender, younger age, and ADHD symptoms. NF1-related somatic factors did not predict behavioral problems scores. Because the rating of behavioral problems by adolescents with NF1 are so different from parent and teacher ratings, the study recommends considering all these three views.

Chapter 5 describes the baseline measurement of the SPOT NF1 study (Dutch acronym for 'Social and Psychological support of people with NF1 in their Teens or twenties'), aiming at finding predictors of mental quality of life of adolescents and young adults with NF1. From 2013 to 2015, in the Netherlands and Belgium, 102 adolescents and young adults (16 to 30 years) with NF1 joined this study. Mental quality of life (MQoL) was measured with the Short-Form Health Survey (SF-36). Vitality, coping with NF1, concentration, physical activity, and internalizing problems had a strong association with MQoL. Women reported a lower MQoL and more fatigue than men did. Mental quality of life was affected more than physical quality of life was. Determinants of mental quality of life were role functioning in physical activities, fatigue, internalizing, and social problems. Next to this, fatigue severely affected quality of life, in women more than in men.

Chapter 6 describes the results of the randomized placebo-controlled NF1-SIMCODA-trial (Simvastatin for cognitive deficits and daily life functioning), in which the efficacy and safety of specific medication (simvastatin) were assessed in a group of school-aged children and adolescents with NF1. In previous research, statins were shown to reduce learning deficits in mice with NF1, but results of a previous trial in children were not clear. We recruited children with NF1 aged 8–16 years from two national referral centers in the Netherlands and Belgium. Children were

randomly assigned to simvastatin treatment or placebo for 12 months. Investigators, participants, and parents did not know in which group the children were placed. Primary outcome measures were full-scale intelligence, attention problems (measured with the CBCL), and internalizing behavioral problems (CBCL). We randomly assigned 84 children to a treatment group (43 to simvastatin, 41 to placebo) between 2010 and 2012. Simvastatin for 12 months had no effect on full-scale intelligence, attention problems, and internalizing behavioral problems. Children on simvastatin or on placebo reported adverse events, which were serious in two and four patients, respectively. Simvastatin treatment during 12 months did not reduce cognitive deficits or behavioral problems in children with NF1. The use of simvastatin for cognitive enhancement in children with NF1 was not recommended.

Chapter 7 evaluates the cognitive and behavioral outcome measures used in the former study in order to find how appropriate the selection of these measures was. We did this by analyzing the degree of deficits compared to reference groups, test-retest reliability, and how scores correlate between outcome measures. Outcome measures were compared with age-specific reference groups to identify domains of dysfunction. The strongest deviations from the reference groups were observed for full-scale intelligence, Rey Complex Figure Test delayed recall, attention problems, and social problems. Test-retest reliability over the 1-year trial period was excellent for intelligence scales, but poor to moderate for other neuropsychological tests and CBCL subscales. The correlation structure revealed two strong components in the outcome measures behavior and cognition, with no correlation between these components. Scores on psychosocial quality of life correlated strongly with behavioral problems and less with cognitive deficits, indicating cognitive and behavioral outcomes are complementary. This analysis demonstrates the need to include reliable outcome measures on a variety of cognitive and behavioral domains in clinical trials for NF1.

Chapter 8 describes the worries in daily life and the needs for care of adults with NF1, using a qualitative design. Follow-up of adults with NF1 often focuses on tumor growth, but follow-up of cognitive or social problems and other NF1-related problems is rarely a part of standardized care. In order to provide optimal care services for these patients, we explored needs for care in adults with NF1. A qualitative study was performed using group interviews, exploring worries and care needs in medical, psychological, and socioeconomic domains, also focusing on the transition from pediatric to adult care. Four focus groups were conducted, including young adult patients, patients over age 30, and parents of young adult patients. In total, 30 patients and 12 parents participated.

The interviews were taken down literally and analyzed by a computer program. Themes were organized using the World Health Organization International Classification of Functioning, disability, and health (ICF). Results indicated many and diverse worries and care needs both during the transitional period and in adulthood in medical, mental health, and socioeconomic domains. Worries could be categorized into 13 themes. Parents reported high stress levels and difficulties with their parental role. Participants expressed the need for more information, access to NF1 experts, daily living support, care for mental health and socioeconomic participation, and closer communication between health-care providers. In conclusion, worries and needs of patients and parents underline the importance of multidisciplinary follow-up and continuity of care during and after the transitional period. Additionally, parental stress requires more attention from care providers.

Discussion and recommendations

This thesis is concluded with a **discussion**, summarizing and critically interpreting the findings, formulating implications and recommendations for future follow-up, treatment, and research. The main contribution of this thesis to the behavioral phenotype of NF1 is due to larger sample sizes, broader outcome measures, the longitudinal study design, and the associations between phenotype and quality of life and participation.

The main recommendations for clinical assessment and treatment are:

- When developmental motor problems are severe, professionals should consider diagnosing DCD (developmental coordination disorder) in NF1.
- Since both cognition and behavior are important features of the behavioral phenotype of NF1, psychological assessment in NF1 should include both aspects.
- Early recognition of anxiety and depression and easy access to mental health care are necessary to prevent lower quality of life and to prevent late or even too late treatment of these serious disorders.
- Attentional and social problems should be a focus of attention in the follow-up of NF1 since these problems interact and can reinforce each other. Children with one or two of these problems are at risk of learning problems, social isolation, and other comorbid psychopathology. Early and regular screening into adulthood can reduce the risk of these consequences.

- Because fatigue is a strong determinant of quality of daily life, this needs to be reflected in assessments and care.
- Current successful symptomatic treatment methods used to treat chronic fatigue may be effective in NF1 and the usefulness of these treatments for NF1 needs to be evaluated.
- The ICF model (the International Classification of Functioning, disability, and health, a way to look at function, activity and participation devised by the World Health Organization) is a useful framework to also look at socioeconomic, personal, and environmental issues in a broad assessment of the needs of people with NF1 and their families.

Suggestions for future research are:

- Future longitudinal and intervention studies may clarify to what extent musculoskeletal or neurodevelopmental problems contribute to the development of motor problems in NF1.
- Future research may explore the reason why language problems occur in both young children with familial NF1 and their parents with NF1.
- To express the severity of NF1 for future research**, i**t would be better not to add or combine somatic, cognitive, emotional, social, and behavioral symptoms into one score, but to consider them as separate predictors of quality of life and participation.
- The recently developed INF1-QOL-Questionnaire could be extended with a question about the effects of fatigue on daily life.
- Future research needs to focus on the development of fatigue in the natural history of NF1.
- Since fatigue is a strong determinant of quality of daily life, future research needs to focus on predictors of fatigue and on trials evaluating the treatment of fatigue in children and adults.
- Syndrome-specific patient reported outcome measures (questionnaires), completed by larger groups of patients and their families from various countries and cultures, can contribute to the knowledge about the relations between behavioral phenotype, quality of life, and participation in daily life.
- Clinically relevant outcome measures are needed when deciding whether a treatment should be given to children with learning difficulties. In a schematic overview, recommendations are formulated regarding instruments that can be used in follow-up and future trials. Research should also focus on accumulating and integrating knowledge about outcome measures to harmonize the selection of neuropsychological outcome measures in research on NF1.

II. **Samenvatting** (Dutch Summary)

Neurofibromatose type 1 (NF1) is een genetische aandoening of syndroom veroorzaakt door veranderingen in het NF1-gen op chromosoom 17q11.2. NF1 komt voor bij 1: 2000 tot 4000 mensen, waarbij ongeveer de helft 'nieuwe mutaties' zijn, wat betekent dat de ouders geen NF1 hebben. NF1 leidt tot symptomen in het uiterlijk van mensen, zoals lichtbruine vlekken op de huid (ook wel café-au-lait-vlekken genoemd), knobbeltjes op of in de huid, maar ook tot een verhoogd risico op goedaardige en kwaadaardige tumoren. Er is een levenslange kans van 7-13% om kwaadaardige tumoren te ontwikkelen kwaadaardige perifere zenuwschade-tumoren te ontwikkelen. De meeste symptomen komen voor in het zenuwstelsel, de huid en de botten. Dit leidt tot veel onvoorspelbare en variabele complicaties. Bij volwassenen lijken geslacht en leeftijd niet samen te hangen met de fysieke ernst van NF1, maar er lijkt wel een verband te bestaan met de algemene kwaliteit van leven. Hoewel de diagnostische criteria grotendeels fysiek zijn en de lichamelijke symptomen ernstig en indrukwekkend zijn, zijn cognitieve en gedragsproblemen de meest voorkomende complicaties van NF1 bij kinderen.

Genotype is een ander woord voor de genetische samenstelling van cellen of van een organisme. Het genotype, samen met andere genetische factoren en omgevingsfactoren, bepaalt iemands fenotype. Het fenotype van een organisme is de combinatie van kenmerken, waaronder uiterlijk en eigenschappen, ontwikkeling en gedrag. Met een gedragsfenotype wordt gedoeld op cognitie, persoonlijkheid en gedrag. Sommige gedragsfenotypes kunnen psychische stoornissen of syndromen zijn. Neurocognitieve en psychosociale diagnostiek kan een profiel van sterke en zwakke punten opleveren, een gedragsfenotype van de cognitieve, zintuiglijke, motorische, educatieve, gedrags-, sociale en emotionele kenmerken van mensen met NF1.

Gedragsfenotype van NF1

Het gemiddelde totale intelligentiequotiënt (IQ) van kinderen met NF1 is ongeveer 10 tot 15 punten lager dan het IQ in de algemene populatie en is ook lager als wordt vergeleken met broers en zussen zonder NF1. Verstandelijke beperking komt tweemaal zo vaak voor bij NF1 en er zijn dus meer mensen met NF1 die een IQ onder 70 hebben. Andere cognitieve problemen bij NF1 hebben te maken met spraak en taal, visueel-ruimtelijke vaardigheden, uitvoerende of 'executieve' functies (inhibitie, planning en flexibiliteit), aandacht en motorische vaardigheden. De meerderheid van de gedragsproblemen bij NF1 betreft emotionele problemen zoals angst, depressie en teruggetrokken gedrag. De meest voorkomende psychische stoornis bij NF1 is ADHD (aandachtsdeficiëntie-/ hyperactiviteitsstoornis): ADHD komt voor bij 30 tot 50% van de kinderen

met NF1 (in vergelijking met 3 tot 5% van de kinderen in de algemene bevolking). Kinderen met NF1 hebben vaak ook minder goede sociale vaardigheden en er is een verhoogd risico op autismespectrumstoornis (ASS).

Gevolgen van NF1 in het dagelijks leven bestaan uit slaapproblemen, leerproblemen en een behoefte aan ondersteuning en behandeling. Zowel de mensen met NF1 zelf als hun ouders en families ervaren hogere niveaus van stress, ook als gevolg van de onzekerheid over het beloop van NF1. Gezondheidsgerelateerde kwaliteit van leven (Quality of Life: QoL) is lager bij kinderen en ouders, vooral als het gaat om (lichamelijke) pijn.

Dit proefschrift heeft tot doel bij te dragen aan de kennis over het gedragsfenotype van NF1 op cognitief, gedragsmatig, emotioneel en sociaal gebied en de gevolgen van dit fenotype op het dagelijkse leven. Door diagnostiek en behandeling te verbeteren kunnen de zorg voor en de kwaliteit van leven van kinderen en volwassenen met NF1 worden verbeterd. De eerste vijf hoofdstukken gaan over motorische, emotionele, gedrags- en cognitieve problemen, vermoeidheid, kwaliteit van leven en participatie (deelname aan het dagelijks leven). Vervolgens wordt deze kennis toegepast in drie studies, de SPOT-studie, de SIMCODA-studie en een kwalitatief onderzoek naar zorgen en zorgbehoeften.

Hoofdstuk 2 richt zich op motorische problemen van kinderen met NF1 en mogelijke voorspellers van die problemen. Deze studie maakt gebruik van een uitgebreide testbatterij van de motorische vaardigheden bij een relatief grote groep kinderen met NF1. Negenenzestig kinderen met NF1, in de leeftijd van 4 tot 16 jaar, kregen een motorisch, psychologisch en neurologisch onderzoek. Motorische prestaties werden gemeten met de M-ABC: Movement Assessment Battery for Children. Eenenzestig procent van deze kinderen scoorde in het klinische bereik van de M-ABC en had dus ernstige motorische problemen. Motorische problemen bleken samen te hangen met ADHD, ASS en externaliserende problemen (regeloverschrijdend gedrag en agressie). Motorische vaardigheid werd niet voorspeld door leeftijd, intelligentie, scoliose, hypotonie of hypermobiliteit. De studie concludeert dat motorische problemen een van de meest voorkomende comorbide ontwikkelingsproblemen bij kinderen met NF1 zijn en deze problemen nemen niet af met de leeftijd. Vanwege hun impact op het dagelijks functioneren moeten motorische problemen specifiek worden aangepakt bij de diagnose, follow-up en behandeling van NF1.

Hoofdstuk 3 is een longitudinale studie van de ontwikkeling van emotionele en gedragsproblemen bij jonge kinderen met NF1 in samenhang met hun intellectuele en taalontwikkeling. Bij het eerste

onderzoek op de peuterleeftijd werd gekeken naar taalvaardigheden, intelligentie en emotionele en gedragsproblemen zoals gerapporteerd door ouders. Het tweede onderzoek op schoolleeftijd keek naar intelligentie en emotionele en gedragsproblemen zoals gerapporteerd door ouders en leraren. Van de 61 kinderen met NF1 (gemiddelde leeftijd 4½ jaar) die meededen aan het eerste onderzoek, kregen 38 kinderen een tweede onderzoek bij een gemiddelde leeftijd van 8 jaar. Psychische problemen die door de ouders werden gezien (angstig, teruggetrokken en depressief gedrag en/of lichamelijke klachten, zogenaamde 'internaliserende problemen') namen significant toe met de leeftijd bij deze groep. Intelligentie en taalvaardigheid hingen niet samen met deze problemen. De studie concludeert dat internaliserende problemen op kleuterleeftijd mogelijk voorspellend zijn voor het zelfde type problemen op schoolleeftijd.

Hoofdstuk 4 is een studie die de emotionele en gedragsproblemen van een grote groep van kinderen en jongeren met NF1 beschrijft. Ouders van 183 kinderen en jongeren met een gemiddelde leeftijd van 11 jaar (van 6 tot 17 jaar) vulden de oudergedragsvragenlijst CBCL in (Child Behavior Checklist). Ook vulden 173 leraren de leerkrachtvragenlijst TRF in (Teacher's Report Form) en 88 jongeren (11 tot 17 jaar) een zelfbeoordelingsvragenlijst (Youth Self Report, YSR). Volgens de ouders had 32% van de kinderen gedrags- en emotionele problemen (vergeleken met 10% in de algemene bevolking). Dit percentage was veel lager volgens de beoordeling door leerkrachten of jongeren zelf. Volgens zowel ouders, leerkrachten en jongeren zelf waren de meeste problemen te zien op de schalen voor lichamelijke klachten, sociale problemen en aandachtsproblemen. Aandachtsproblemen hingen samen met lager verbaal IQ, mannelijk geslacht, jongere leeftijd en ADHD-symptomen. NF1-gerelateerde lichamelijke factoren waren niet voorspellend voor psychische problemen. Omdat de beoordelingen van psychische problemen bij jongeren met NF1 door ouders, leerkrachten en jongeren zelf zulke verschillende resultaten oplevert wordt aanbevolen om steeds informatie in te winnen bij alle drie de informanten.

Hoofdstuk 5 beschrijft de nulmeting van het SPOT NF1-onderzoek ('Sociale en Psychologische Ondersteuning van Tieners en twintigers met NF1'), gericht op het vinden van voorspellers voor de mentale kwaliteit van leven van jongeren en jongvolwassenen met NF1. Vanaf 2013 tot 2015 deden in Nederland en België 102 jongeren en jonge volwassenen (16 tot 30 jaar) met NF1 mee aan dit onderzoek. Mentale levenskwaliteit (MQoL) werd gemeten met de Short-Form Health Survey (SF-36). Vitaliteit, omgaan met NF1, concentratie, fysieke activiteit en internaliserende problemen hingen sterk samen met MQoL. Vrouwen rapporteerden een lagere MQoL en meer vermoeidheid dan mannen. Mentale kwaliteit van leven bleek meer aangedaan dan fysieke

kwaliteit van leven. Voorspellers van mentale kwaliteit van leven zijn rol-functioneren bij fysieke activiteiten (het kunnen uitvoeren van taken die men bij zijn rol vindt horen), vermoeidheid, internaliserende en sociale problemen. Vermoeidheid heeft grote invloed op de kwaliteit van leven, bij vrouwen meer dan bij mannen.

Hoofdstuk 6 beschrijft de resultaten van de gerandomiseerde placebo-gecontroleerde NF1-SIMCODA-studie (Simvastatine voor cognitieve problemen en het functioneren in het dagelijks leven), waarin de werkzaamheid en veiligheid van specifieke medicatie (simvastatine) werd beoordeeld bij een groep schoolgaande kinderen en jongeren met NF1. In eerder onderzoek werd aangetoond dat statines de leerproblemen van muizen met NF1 verminderen, maar de resultaten van een onderzoek bij kinderen waren niet duidelijk. Deelnemers waren kinderen met NF1 in de leeftijd van 8-16 jaar uit twee nationale centra in Nederland en België. Kinderen werden willekeurig toegewezen aan simvastatine-behandeling of placebo gedurende 12 maanden. Onderzoekers, deelnemers en ouders wisten niet in welke groep de kinderen werden geplaatst. Primaire uitkomstmaten waren totale intelligentie (gemeten met een intelligentietest), aandachtsproblemen en internaliserende problemen (beide gemeten met de CBCL). Tussen 2010 en 2012 werden 84 kinderen voor deze trial willekeurig verdeeld over de beide behandelgroepen (43 simvastatine, 41 placebo). Het toedienen van simvastatine gedurende 12 maanden had geen effect op totale intelligentie, aandachtsproblemen of internaliserende problemen. Kinderen in de simvastatine- of de placebogroep hadden beide bijwerkingen, die respectievelijk ernstig waren bij twee en vier kinderen. Simvastatine-behandeling gedurende 12 maanden vermindert niet de cognitieve tekorten of psychische problemen bij kinderen met NF1. Het gebruik van simvastatine voor verbetering van de cognitie bij kinderen met NF1 wordt niet aanbevolen.

Hoofdstuk 7 evalueert de cognitieve en gedragsmatige uitkomstmaten die werden gebruikt in de vorige studie om te bepalen hoe goed de keuze van deze instrumenten was. We deden dit door de ernst van de problemen te vergelijken met die van leeftijdsgenoten uit de normgroepen, door te bekijken wat de test-hertest-betrouwbaarheid was en hoe de verschillende instrumenten met elkaar samenhingen. De sterkste afwijkingen van de normgroep werden gezien op de schaal voor totale intelligentie, de Rey Complexe Figuur Test-uitgestelde herinnering, aandachtsproblemen en sociale problemen. Test-hertest-betrouwbaarheid over de trial-periode van één jaar was uitstekend voor intelligentietests, maar slecht tot matig voor de neuropsychologische tests en de CBCL-subschalen. De correlatiestructuur gaf twee sterke componenten in de instrumenten te zien: één component voor gedrag en één voor cognitie, zonder correlatie tussen die beide

componenten. Scores op psychosociale kwaliteit van leven hingen sterk samen met psychische problemen en minder met cognitieve problemen. Instrumenten voor cognitie en psychische problemen zijn klaarblijkelijk complementair. Deze analyse geeft aan dat betrouwbare instrumenten nodig zijn die een verscheidenheid van cognitieve en psychische problemen in kaart brengen bij klinische trials voor NF1.

Hoofdstuk 8 beschrijft de zorgen in het dagelijks leven en de zorgbehoeften van volwassenen met NF1 met behulp van een kwalitatieve studie. Opvolging (follow-up) van volwassenen met NF1 richt zich vaak op tumorgroei, maar de follow-up van cognitieve of sociale problemen en andere NF1-gerelateerde problemen is vaak geen standaard-onderdeel van de zorg. Om optimale zorg te bieden aan mensen met NF1 hebben we de zorgbehoeften van volwassenen met NF1 onderzocht. Er werd kwalitatief onderzoek gedaan met behulp van groepsinterviews waarin zorgen en zorgbehoeften in kaart werden gebracht op lichamelijk, psychologisch en sociaal-economisch gebied, ook gericht op de overgang (transitie) van pediatrische naar volwassen zorg. Er werden sessies gehouden met vier afzonderlijke focusgroepen: jongvolwassen patiënten, patiënten ouder dan 30 jaar en ouders van jongvolwassen patiënten. In totaal namen 30 patiënten en 12 ouders deel. De interviews werden letterlijk vastgelegd en geanalyseerd met behulp van een computerprogramma. Thema's werden georganiseerd met behulp van de World Health Organisatie Internationale Classificatie van Functie, beperking en gezondheid (ICF). Er waren veel en uiteenlopende zorgen en behoeftes aan zorg zowel tijdens de transitie als op volwassen leeftijd op somatisch-, geestelijke gezondheid- en sociaal-economisch gebied. Zorgen kunnen worden onderverdeeld in 13 thema's. Ouders rapporteerden hoge stressniveaus en moeilijkheden bij het vervullen van hun ouderlijke rol. Deelnemers gaven aan behoefte te hebben aan meer informatie, toegang tot NF1-experts, ondersteuning in het dagelijks leven, zorg voor de geestelijke gezondheid en sociaal-economische participatie en betere communicatie tussen zorgverleners. De zorgen en behoeften van patiënten en ouders onderstrepen het belang van multidisciplinaire follow-up en continuïteit van zorg tijdens en na de transitie. Daarnaast verdient ouderlijke stress meer aandacht van zorgverleners.

Discussie en aanbevelingen

Dit proefschrift wordt afgesloten met een discussie, een samenvatting en een kritische interpretatie van de bevindingen, maar ook met implicaties en aanbevelingen voor toekomstige follow-up, behandeling en onderzoek. Dit proefschrift draagt bij aan het gedragsfenotype van NF1,

wat vooral te danken is aan een grotere omvang van de steekproeven, bredere uitkomstmaten, het longitudinale studiedesign en de verbanden tussen fenotype en kwaliteit van leven en participatie.

De belangrijkste aanbevelingen voor diagnostiek en behandeling zijn:

- Als motorische ontwikkelingsproblemen ernstig zijn, zouden professionals DCD (developmental coordination disorder; ontwikkelingscoördinatiestoornis) als comorbide probleem moeten diagnosticeren in NF1.
- Aangezien zowel cognitie als gedrag belangrijke kenmerken zijn van het gedragsfenotype van NF1, moet psychologische diagnostiek bij NF1 beide aspecten omvatten.
- Vroegtijdige onderkenning van angst en depressie en goede toegang tot geestelijke gezondheidszorg is noodzakelijk om een lagere kwaliteit van leven en late of zelfs te late behandeling van deze ernstige problemen te voorkomen.
- Aandachts- en sociale problemen moeten een aandachtspunt zijn in de follow-up van NF1 omdat deze problemen elkaar kunnen versterken. Kinderen met één of twee van deze problemen lopen het risico op leerproblemen, sociaal isolement en andere comorbide psychopathologie. Vroege en regelmatige screening onderweg naar volwassenheid kan de kans op deze gevolgen verminderen.
- Omdat vermoeidheid een sterke bepalende factor is voor de kwaliteit van het dagelijks leven, moet dit tot uiting komen in diagnostiek en zorg voor NF1.
- Huidige succesvolle symptomatische behandelingsmethoden die worden gebruikt om chronische vermoeidheid te behandelen kunnen effectief zijn bij NF1 en de bruikbaarheid van deze behandelingen voor NF1 moet worden geëvalueerd.
- Het ICF-model van de Wereldgezondheidsorganisatie (WHO), een manier om te kijken naar functie, activiteit en participatie, is een nuttig kader om ook te kijken naar de sociaal-economische, persoonlijke en omgevingsinvloeden bij een brede beoordeling van de behoeften van mensen met NF1 en hun families.

Suggesties voor toekomstig onderzoek zijn:

- Toekomstige longitudinale en interventiestudies kunnen verduidelijken in welke mate neurologische ontwikkelingsproblemen en problemen van het houdings- en bewegingsapparaat bijdragen tot de ontwikkeling van motorische problemen bij NF1.

- In toekomstig onderzoek kan de oorzaak worden gezocht van taalproblemen bij jonge kinderen met NF1 van wie de ouders ook NF1 hebben.
- Om de ernst van NF1 weer te geven, zou het beter zijn om fysieke, cognitieve, emotionele, sociale en gedragssymptomen niet in één score samen te vatten of te combineren, maar om ze te beschouwen als afzonderlijke voorspellers van kwaliteit van leven en participatie.
- De recent ontwikkelde INF1-QOL-vragenlijst kan worden uitgebreid met een vraag over de effecten van vermoeidheid op het dagelijks leven.
- Toekomstig onderzoek moet zich richten op de ontwikkeling van vermoeidheid in het natuurlijk beloop van NF1 bij kinderen en volwassenen.
- Aangezien vermoeidheid een sterke bepalende factor is voor de kwaliteit van het dagelijks leven, moet toekomstig onderzoek zich richten op voorspellers van vermoeidheid en op studies die de behandeling van vermoeidheid evalueren.
- Syndroom-specifieke door de patiënt zelf in te vullen uitkomstmaten (vragenlijsten, zogenaamde PROM's), ingevuld door grotere groepen patiënten en hun families uit verschillende landen en culturen, kunnen bijdragen aan de kennis over de relaties tussen gedragsfenotype, kwaliteit van leven en deelname aan het dagelijks leven.
- Klinisch relevante uitkomstmaten zijn nodig om te beslissen of een behandeling moet worden gegeven aan kinderen met leer- en gedragsproblemen. In een schematisch overzicht worden aanbevelingen geformuleerd met betrekking tot instrumenten die kunnen worden gebruikt in follow-up en toekomstige trials. Onderzoek moet ook gericht zijn op het verzamelen en integreren van kennis over uitkomstmaten om de selectie van neuropsychologische uitkomstmaten in onderzoek bij NF1 te harmoniseren.

III. Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ADOS-G	Autism Diagnostic Observation Scale-Generic
ASD	Autism spectrum disorder
Aseba	Achenbach System of Empirically Based Assessment
CBCL	Child behavior checklist
CHQ-PF50	Child Health Questionnaire CHQ–parent form 50
CI	Confidence interval
CNL	Kempenhaeghe Centre for Neurological Learning Disabilities
CWT	Color-Word interference task
DCD	Developmental coordination disorder
DSM-IV	Diagnostic and statistical manual of mental disorders
EF	Executive functions
ENCORE	Erfelijke Neurocognitieve Ontwikkelingsstoornissen Rotterdam Erasmus MC
Erasmus MC	Erasmus Medical Center
GP	General practitioner
HCP	Health-care provider
HRQoL	Health-related Quality of Life
ICF	International classification of functioning, disability, and health
ID	Intellectual disability
IQ	Intelligence quotient
ISCED	International classification of education

KMO	Kaiser-Meyer-Olkin
JLO	Judgement of Line Orientation
LCQ	Language comprehension quotient
M-ABC-1 or 2	Movement Assessment Battery for Children version 1 or 2
MEC	Medical and Ethical Review Committee
MPNST	Malignant peripheral nerve sheath tumor
MQoL	Mental quality of life
NF1	Neurofibromatosis type 1
NF1-SIMCODA	Simvastatin for cognitive deficits and behavioral problems in patients with neurofibromatosis type 1
NFVN	Neurofibromatosis patient organization of The Netherlands
QoL	Quality of life
PCA	Principal components analysis
Ras	Rat Sarcoma protein
RCFT	Rey Complex Figure test
RDLS	Reynell developmental language scales
SD	Standard deviation
SDQ	Sentence development quotient
SELT	Schlichting expressive language test
SES	Socioeconomic status
SF-36	Short-Form Health Survey
SON-R 2½-7	Snijders Oomen non-verbal revised intelligence scale for young children

SPOT-NF1	Sociale en Psychische ondersteuning van Tieners en twintigers met NF1
SRS	Social Responsiveness Scale
TRF	Teacher's Report Form
VOLG	Vroegtijdige Onderkenning Leer- en Gedragsproblemen
WDQ	Word development quotient
WISC-III-NL	Wechsler intelligence scale for children, third version for the Netherlands
WHO	World Health Organization
WPPSI-III-R	Wechsler Preschool and Primary Scale of Intelligence-Third version for the Netherlands
YSR	Youth self-report

IV. Authors and affiliations

Aarsen FK, PhD	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
van Abeelen S	Kempenhaeghe Centre for neurological learning disabilities, Heeze, The Netherlands
Bongers S	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Both PH	Intellectual Disability Medicine, Department of General Practice, Erasmus Medical Center, Rotterdam, the Netherlands
Bouman CP	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Catsman-Berrevoets CE, PhD*	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Descheemaeker M-J	Centre for Human Genetics, University Hospital Leuven, Belgium
Van Eeghen AM, PhD*	Intellectual Disability Medicine, Department of General Practice, Erasmus Medical Center, Rotterdam, the Netherlands and The Hartekamp Group, Care and Service for People with Intellectual Disabilities, Haarlem, the Netherlands
Elgersma Y, PhD*	Department of Neuroscience, Erasmus Medical Center, Rotterdam, The Netherlands
Franken M-CJP, PhD	Department of Otorhinolaryngology, Erasmus MC- Sophia Children's Hospital, Rotterdam, The Netherlands

Gaukema E	Kempenhaeghe Centre for neurological learning disabilities, Heeze, The Netherlands
Van Helden H	Intellectual Disability Medicine, Department of General Practice, Erasmus Medical Center, Rotterdam, the Netherlands
Hendriksen JG, PhD	Kempenhaeghe Centre for neurological learning disabilities, Heeze, The Netherlands
Krab LC, PhD	Department of Neuroscience, Erasmus Medical Center, Rotterdam, The Netherlands
Legerstee JS, PhD*	Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Legius E, PhD	Department of Human Genetics, Catholic University Leuven and Centre for Human Genetics, University Hospital Leuven, Belgium
Looman CWN, Ir	Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands
Moll HA, PhD*	Department of General Pediatrics, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Nicholson BA	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
van Noort K	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
De Nijs PFA, PhD*	Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Oostenbrink R, PhD*	Department of General Pediatrics, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Plasschaert E, PhD	Department of Human Genetics, Catholic University Leuven and Centre for Human Genetics, University Hospital Leuven, Belgium

Renard M, PhD	Department of Paediatrics, University Hospital Leuven, Belgium
Rietman AB*	Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands
Van Staa AL, PhD	Research Center Innovations in Care, Rotterdam University of Applied Sciences, Rotterdam, the Netherlands
Taal W, PhD*	Department of Neuro-Oncology/Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
Van der Vaart M, PhD*	Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
Vergouwe Y, PhD	Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands
Vogels A, PhD	Department of Human Genetics, Catholic University (KU), Leuven, Belgium
De Wit MCY, PhD*	Department of Pediatric Neurology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands

***** Currently also participating in **ENCORE** Expertise Center for Neurodevelopmental Disorders, Erasmus Medical Center, Rotterdam, The Netherlands

V. List of Publications

(In chronological order of publication)

Within this thesis

van der Vaart T, Plasschaert E, Rietman AB, Renard M, Oostenbrink R, Vogels A, de Wit MC, Descheemaeker MJ, Vergouwe Y, Catsman-Berrevoets CE, Legius E, Elgersma Y, Moll HA. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial (2013). Lancet Neurol 2013;12:1076-1083.

van der Vaart T, Rietman AB, Plasschaert E, Legius E, Elgersma Y, Moll HA, NF1-SIMCODA Study Group (2016). Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology 2016;86:154-160.

Rietman AB, Van der Vaart M, Plasschaert E, Nicholson BA, Oostenbrink R, Krab LC, Descheemaeker MJ, De Wit MCY, Moll HA, Legius E, De Nijs PFA (2017). Emotional and behavioral problems in children and adolescents with neurofibromatosis type 1. Am J Med Genet B Neuropsychiatr Genet 2018;177:319-328.

Rietman AB, Oostenbrink R, Bongers S, Gaukema E, van Abeelen S, Hendriksen JG, Looman CWN, de Nijs PFA, de Wit MC (2017). Motor problems in children with neurofibromatosis type 1. J Neurodev Disord 2017;9:19

Rietman AB, Oostenbrink R, van Noort K, Franken MJP, Catsman-Berrevoets CE, Aarsen FK, Hendriksen JG, de Nijs PFA (2017). Development of emotional and behavioral problems in neurofibromatosis type 1 during young childhood. Am J Med Genet A 2017;173:2373-2380.

Rietman AB, Van Helden H, Both PH, Taal W, Legerstee JS, Van Staa AL, Moll HA, Oostenbrink R, Van Eeghen AM (2017). Worries and Needs of Adults with Neurofibromatosis type 1 and Parents. Am J Med Genet A 2018;176:1150-1160.

Rietman AB, Bouman CP, Oostenbrink R, Plasschaert E, Descheemaeker M-J, de Wit MCY, Legius E, Moll HA (2019). Predictors of mental quality of life of adolescents and young adults with neurofibromatosis type 1. S*ubmitted.*

International publications outside this thesis

Taal M, Rietman AB, Van der Meulen S, Schipper M, Dejonckere, PH (2013). Children with specific language impairment show difficulties in sensory modulation. *Logopedics Phoniatrics Vocology.*

Overwater IE, Rietman AB, Elgersma Y, de Wit MCY (2013). Treatment of intractable epilepsy in TSC with everolimus not yet evidence-based. *Annals of Neurology.*

Overwater IE, Bindels-de Heus K, Rietman AB, Ten Hoopen LW, Vergouwe Y, Moll HA, de Wit MC (2015). Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs. *Epilepsia*.

Overwater IE; Rietman AB; Bindels - de Heus GCB; Looman CWN; Rizopoulos D; Sibindi TM; Perumpillichira JC; Jansen FE; Moll HA; Elgersma Y; de Wit MCY (2016). Sirolimus for epilepsy in children with Tuberous Sclerosis Complex: a randomized controlled trial. *Neurology.*

Walsh KS, Janusz J, Wolters PL, Moll HA, van der Vaart T, Rietman AB (2016). Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. *Neurology*.

Schiller RM, IJsselstijn H, Madderom MJ, Rietman AB, Smits M, van Heijst AFJ, Tibboel D, White T, Muetzel RL (2017). Neurobiological Correlates of Attention and Memory Deficits Following Critical Illness in Early Life. *Critical Care Medicine*.

Leeuwen L, Schiller RM, Rietman AB, van Rosmalen J, Wildschut ED, Houmes RJM, Tibboel D, IJsselstijn H (2017). Risk Factors of Impaired Neuropsychologic Outcome in School-Aged Survivors of Neonatal Critical Illness. *Critical Care Medicine.*

Eijk S, Mous SE, Dieleman GC, Dierckx B, Rietman AB, de Nijs PFA, Ten Hoopen LW, van Minkelen R, Elgersma Y, Catsman-Berrevoets CE, Oostenbrink R, Legerstee JS (2018). Autism Spectrum Disorder in an Unselected Cohort of Children with Neurofibromatosis Type 1 (NF1). *Journal of Autism and Developmental Disorders*.

Both PH, ten Holt L, Mous SE, Patist J, Rietman AB, Dieleman GC, ten Hoopen L, Vergeer M, de Wit MCY, Bindels-de Heus GCB, Moll HA, van Eeghen, AM (2018). Tuberous sclerosis complex. *Epilepsy and Behavior*.

Overwater IE, Rietman AB, Mous SE, Bindels-de Heus GCB, Rizopoulos D, ten Hoopen LW, van der Vaart M, Jansen FE, Elgersma Y, Moll HA, de Wit MCY (2019). Randomized, double-blind, placebo-controlled trial of everolimus for intellectual disability, neuropsychological deficits, and autism in Tuberous Sclerosis Complex. *Neurology.*

Schiller RM , Madderom MJ , van Rosmalen, JM , van Heijst, AFJ , de Blaauw, I , Utens, EMWJ, Rietman, AB, Verhulst, FC, Tibboel, D , White, TJH and IJsselstijn, H (2018). Working-memory training following neonatal critical illness. *Critical Care Medicine*.

Berghmans JM, Poley MJ, van der Ende J, Rietman AB, Glazemakers I, Himpe D, Verhulst FC, Utens E (2018). Changes in sensory processing after anesthesia in toddlers. *Minerva Anesthesiology*.

Marchal JP, de Vries M, Conijn J, Rietman AB, IJsselstijn H, Tibboel D, Haverman L, Maurice-Stam H, Oostrom KJ, Grootenhuis MA (2019). Pediatric Perceived Cognitive Functioning: Psychometric Properties and Normative Data of the Dutch Item Bank and Short Form. *Journal of the International Neuropsychological Society.*

Overwater IE, Rietman AB, Mous SE, Bindels-de Heus K, Rizopoulos D, ten Hoopen LW, van der Vaart T, Jansen FE, Elgersma Y, Moll HA, de Wit MCY on behalf of the ENCORE Expertise Centre for Neurodevelopmental Disorders (2019). A randomized controlled trial with everolimus for IQ and autism in tuberous sclerosis complex. *Neurology.*

Hijkoop A, Rietman AB, Wijnen RMH, Tibboel D, Cohen-Overbeek TE, van Rosmalen J, IJsselstijn H (2019). Gastroschisis at school age: what do parents report? *European Journal of Paediatrics.*

Publications in Dutch

Rietman AB (1999). *Werken met aandacht- een neuropsychologische benadering van de werkhouding*. Vlissingen: Bazalt/HCO.

Rietman AB (2011). Neurofibromatose onder de loep. *Balans Magazine*.

Rietman AB (2013). Praten met kinderen over NF1. *Nieuwsflits* 2013, nummer 1. Den Haag: NFVN.

Dunn, W. (2013). Vertaling, herziening en bewerking door A.B. Rietman. *Leven met sensaties- begrijp je zintuigen.* Amsterdam: Pearson.

Dunn, W. (2013). Vertaling, herziening en bewerking door A.B. Rietman. *Sensory Profile-NL, Handleiding bij Nederlandse versie van de SP*. Amsterdam: Pearson.

Rietman AB (2014). *Niet altijd zichtbaar-* Sociaal emotionele en leerproblemen bij kinderen en jongeren met NF1. Publieksbrochure. Den Haag: NFVN.

Rietman AB (2015). *Praten met kinderen over TSC* (TSC Contact).

Neurofibromatose Vereniging Nederland (NFVN; 2015). *Zorgstandaard Neurofibromatose type 1.*

de Wit MCY, Jansen FE, Zylicz SA, van Veelen MLC, Lindhout D, van den Ouweland AMW, Bindels-de Heus GCB, Frohn-Mulder IME, Pasmans SGMA, de Kort GAP, Scheepe JR, ten Hoopen LW, van Steensel MAM, Naus-Postema NC, van Zuilen AD, Zonnenberg BA, Rietman AB, Mulder JC, Wagenaar J. (2015). Tubereuze Sclerose Complex. Richtlijn inzake Diagnostiek, Follow-up en Behandeling. *Tijdschrift voor Neurologie & Neurochirurgie*, 116(1): Supplement, 1-40

Rietman AB, Moll HA, Oostenbrink R (2016). *Spotlicht op jongeren met NF1*. Publieksbrochure. Den Haag: NFVN.

De Ranitz-Gobel M, Oostenbrink R, Rietman AB, Taal W (2016). *Daisy, dat is meteen een heel verhaal.* Den Haag: NFVN.

Rietman AB, ten Hoopen L (2017). Is Een Ziekte 'Echt' En Een Stoornis Niet? *Kind en Adolescent Praktijk*.

Zeidler S, Rietman AB, Dierckx B, Lubbers K, Lincke CR, van Eeghen AM, Kievit A, Douwes B (2017). *Leidraad voor diagnostiek en behandeling van Kinderen met het fragiele X-syndroom.* http://nvavg.nl/wp-content/uploads/2016/02/2017-Leidraad_FraX_syndroom.pdf

Zeidler S, Dierckx B, Lubbers K, van Eeghen AM, Lincke CR, Kievit A, Willemsen R, Rietman AB (2018). Fragiele X-syndroom: nieuwe therapeutische strategieën. *Tijdschrift voor psychiatrie.*

Douwes B, Holleman R, Snelders Y, Dierckx B, Dieleman GC, Lincke CR, Rietman AB, Zeidler S, van Eeghen AM, Kievit JA (2018). *Kwaliteitsstandaard/Richtlijn Fragiele X Syndroom*. https://zichtopzeldzaam.nl/documenten/fragiele-x-syndroom-kwaliteitsstandaard/. Bijbehorende patiënten informatie: https://zichtopzeldzaam.nl/documenten/patienteninformatie-fragiele-x-syndroom/

Van Cranenburgh et al (2018, vijfde herziene druk). *Neuropsychologie, over de gevolgen van hersenbeschadiging.* Hoofdstuk 'Kinderneuropsychologie' door Albert Gramsbergen en André Rietman. Houten: Bohn, Stafleu en van Loghum.

Erasmus MC
Universitair Medisch Centrum Rotterdam

VI. PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Andre B. Rietman Erasmus MC Department: Pediatric Neurology/Child and adolescent psychiatry/psychology Research School: NIHES		PhD period: 2010-2018 Promotors: Prof. Dr. Y. Elgersma; Prof. Dr. H.A. Moll Co-promotors: Dr. P.F.A. de Nijs; Dr. M.C.Y. de Wit

1. PhD training

	Year	Workload Hours	Workload ECTS
General courses			
- Erasmus Winter Programme: Biostatistics for clinicians and Introduction to clinical research	2009	2*25 =50	
- The why and how of readable articles	2011	8	
- Research Integrity- ethics in medical research	2011		2 ECTS
- Biostatistical methods 1	2013		6 ECTS
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2012	20	
- Biomedical English Writing and Communication	2014		3 ECTS
Specific courses (e.g. Research school, Medical Training)			
- Training ADOS 1/2 and ADOS 3/4 (both certified)	2013	3*13 = 39	
- Consensus meeting ADOS	2012-2018	8*2.5 = 20	
Seminars and workshops			
- Endnote en literatuurzoeken- Bibliotheek Erasmus MC	2010	6	
- Symposium NVKN	2010	7	
- CPO-symposium Erasmus MC 'Methodologie van patiëntgebonden onderzoek en voorbereiding subsidieaanvragen'	2011 2013	3 11	
- Training transitie, zelfmanagement en participatie	2011-2016	8*3 = 24	
- Dutch ADHD network	2012-2018	8*1 = 8	
- Colloquia kinder- en jeugdpsychiatrie- en psychologie	2012-2018	4*8= 32	
- Conferentie Ned. Vereniging Neuropsychologie	2011; 2012	2*8= 16	
- Annual clinical symposium Kempenhaeghe	2018	2*8= 16	
- European pediatric psychology conference Gent	2016-2018	2*8= 16	
- Courses on supervising			
Subtotal education		276 =10 ECTS	11 ECTS
Presentations in the Netherlands, Dutch meetings			
- Presentations on current research in ENCORE meetings, internal research meetings, patient meetings (NFVN, STSN and Fragile X association), EAA werkgroepen, kinderartsencongres, schoolpsychologencongres, autismecongres, etc.	2011-2018	9*3= 27	
- Samen Nog Beter Congres- 'Sensorische informatieverwerking' (oral keynote)	2015		1 ECTS
- Revalidatiecongres Den Haag	2016		1 ECTS
- Nederlands psychiatrie jaarcongres NVVP	2015&2016		2 ECTS
- Nederlands congres prikkelverwerking	2017		1 ECTS
Presentations on (Inter)national conferences			
- European conference on Neurofibromatosis (NF1) Oslo (oral)	2010		1 ECTS
- European workshop on NF1 Leuven (oral)	2011		1 ECTS

- European conference on NF1 Istanbul (incl. poster)	2012		1 ECTS
- Conf. Society of behavioral phenotypes (SSBP) Leuven (oral)	2012		1 ECTS
- Behavioral problems in Angelman Syndrome- International Angelman congress Erasmus MC Rotterdam (oral)	2012		1 ECTS
- Autism in Fragile X syndrome- Fragile X Association the Netherlands (oral)	2012		1 ECTS
- Sensory-motor problems, pediatricians week Erasmus MC Sophia Rotterdam (oral)	2013		1 ECTS
- Problems in learning and behavior in NF1, mini-symposium child and adolescent psychiatry and psychology, Erasmus MC Rotterdam (oral)	2013		1 ECTS
- European conference on Sensory processing Finland (oral and poster)	2014		2 ECTS
- European conference on Neurofibromatosis (NF1) Barcelona (oral)	2014		1 ECTS
- Pediatric psychology network- conference Amsterdam (oral)			
- SSBP (society of behavioral phenotypes) conference London (oral)	2014		1 ECTS
	2015		1 ECTS
- ICNC 14th International Child Neurology Congress A'dam (oral)	2016		1 ECTS
- European conference on Neurofibromatosis (NF1) Padua (oral)	2016		1 ECTS
- SSBP conference Leiden (oral)	2017		1 ECTS
- Angelman conference Phoenix Arizona (oral)	2017		1 ECTS
- NVKN jaarcongres Rotterdam (oral)	2018		1 ECTS
- Joint global neurofibromatosis conference 2018 Paris (oral)	2018		1 ECTS
Subtotal conferences		27 = 1 ECTS	24 ECTS
2. Teaching	**Year**	**Hours**	**ECTS**
Lecturing			
- Yearly lectures, workshops, and courses on (neuro)psychological, neurological and therapeutical topics for physicians, psychologists, therapists, teachers, parents, etc.	2010-2018	Approx. 50*6= 300	
- Teaching medical students and psychiatrists in training about neuropsychology, neurofibromatosis type1, language- and learning disorders, regulation disorders, sensory-motor problems, and ADHD	2015-2018		
Supervising, Tutoring			
- Supervising master's clinical or research internships (12 students)	2012-2018		11 ECTS
- Supervising school psychologists and Gz-psychologists in-training (12 students)	2012-2018		11 ECTS
Supervising Master's theses			
- Supervising master's theses (8 students)	2012-2018		8 ECTS
Other			
- Dutch publications on Neurofibromatosis, Tuberous sclerosis, Sensory processing and Psychopathology	2011-2018		4 ECTS
- Collaborating in writing Guideline Tuberous Sclerosis, Standards of care for Neurofibromatosis type 1 and type 2, Brochures for GP's about Neurofibromatosis type 1 and for Fragile X syndrome	2014-2018		2 ECTS
Subtotal Teaching		180 hours = 11 ECTS	36 ECTS
TOTAL		22 ECTS	71 ECTS
(1 ECTS = 28 HOURS)			93 ECTS

Total:

- Education 21 ECTS
- Conferences 25 ECTS
- Teaching 47 ECTS
- **TOTAL** **93 ECTS**

VII. Dankwoord

In 2009 werkte ik nog bij Kinderhaven toen me werd gevraagd mee te denken bij de aanvang van expertisecentrum ENCORE en de trials die werden opgestart. Toen ik in 2010 bij het Erasmus MC kwam werken, was nog niet helemaal duidelijk dat er een promotietraject voor me in zou zitten en hoe dat vorm zou moeten krijgen, maar wel wat mijn rol binnen de trials zou zijn. Ook werd me door de klinisch werkende mensen al snel duidelijk gemaakt dat er meer van me werd verwacht dan alleen een bijdrage aan de trials, maar dat mijn meerwaarde moest liggen in het leggen van verbanden tussen wetenschap en de (poli)klinische praktijk. In de loop van de tijd werd steeds duidelijker dat NF1 en TSC mijn focus moesten zijn en door van alles en nog wat aan te pakken, kreeg mijn promotietraject op een nogal organische manier steeds meer vorm. Bij elkaar heeft het me (fulltime gerekend) ruim 5 jaar gekost om tot dit eindproduct te komen en hoewel ik blij ben deze punt te zetten, ben ik voor mijn gevoel nog maar net begonnen met onderzoek en voelt het meer als een komma.

Hoewel een promotietraject een soloproject lijkt, zijn er veel mensen die een bijdrage hebben geleverd aan dit werk. Met de kans dat ik iemand ga vergeten, wil ik er een paar noemen die ik zonder meer dankbaar ben.

Allereerst alle kinderen, jongeren en volwassenen met Neurofibromatose type 1 (NF1) en hun ouders en verzorgers. Niet alleen waren zij op zoek naar ondersteuning of hulp bij alle gevolgen van NF1. Ook waren ze geregeld onbaatzuchtig bereid om ‘de wetenschap’ van dienst te zijn. ‘Als mijn kind of ik er zelf niet iets aan heb, dan misschien wel een van die andere mensen met NF1, nu of later’. De vriendelijkheid waar in het begin van dit boek wordt gesproken is geregeld zonder meer van toepassing op mensen met NF1. Aan alle mensen met NF1 en aan de mensen om hen heen is dit boek in de eerste plaats opgedragen.

En dan de mensen die aan de start van dit project stonden: Ype Elgersma, mijn promotor van het eerste uur. Hoewel je zo bescheiden was om je terug te trekken uit een aantal van mijn projecten, heb je toch flinke invloed gehad door je duidelijke uitleg, je rustige leiderschap en je inhoudelijke inbreng in vele projecten. Henriëtte Moll, wij hadden al flink wat met elkaar te maken gehad bij het op poten zetten van de VOLG en de SPOT-projecten. Daarom ben ik blij dat je uiteindelijk ook mijn promotor hebt willen zijn. En Willem Frans Arts: helaas was ik niet zo snel dat

je mijn promotor kon blijven, maar je vertrouwen bij de aanvang van ENCORE heeft er mede voor gezorgd dat ik dit werk kon gaan doen. Daarom vind ik het erg leuk dat je de rector wilt vervangen bij mijn promotieplechtigheid.

Aan mijn copromotoren heb ik minstens zo veel te danken. Pieter, mijn directe collega binnen de KJPP (kinder- en jeugdpsychologie/psychiatrie), aan jou heb ik veel gehad tijdens onze (on)geregelde gesprekken, je krabbels in de zijlijn, maar ook door je oog voor detail. Dank voor je beschikbaarheid, je relativeringsvermogen en de gesprekken in welke taal dan ook. Dankzij jou hoeft niemand zich zorgen te maken over een gebrek aan weetjes en verhalen tijdens lunches en borrels. Marie-Claire, van mijn start in de kinderneurologie tot nu was je ondanks je drukke werk steeds in staat om mij te spreken of van commentaar te voorzien met je gevoel voor 'de grote lijn'.

Alle mensen van wie ik binnen ENCORE veel heb geleerd. Als psycholoog had ik aanvankelijk sterk het gevoel dat de wereld van fundamenteel onderzoek ver van mijn bed is. Inmiddels staat (in ieder geval voor mij) de wereld van muizen, genen en moleculen een stuk minder ver af van de wereld van kinderen en kwaliteit van leven.

Mijn collega promovendi, hoewel ik een beetje ouder ben dan jullie, heb ik me bij jullie altijd thuis gevoeld. Thijs, dank voor al onze discussies, je scepsis (door sommigen aangezien voor arrogantie;) en je persoonlijke betrokkenheid en dank voor de eer om je paranimf te mogen zijn! Lieve Iris, geweldig om met jou samen te werken aan de RATE en de RAPIT studies. Ondanks jouw bescheidenheid en je zachtmoedigheid was ik niet verrast door jouw briljante verdediging bij je promotie. Myrthe, je onzekerheid bij de aanvang van jouw promotietraject was zo onterecht, dat heb je wel bewezen door jouw slimme en consciëntieuze manier van werken. Met jouw gedrevenheid gaat het je zeker lukken om ook ver van hier jouw promotie af te ronden.

Alle coauteurs en collega's die hebben meegedacht en meegeschreven aan de artikelen in dit boek. Het is geen onverdeeld genoegen om jullie commentaar binnen te krijgen, omdat het daarna weer veel werk is om dat te verwerken, zowel emotioneel, cognitief als in letters. Allereerst moet ik Rianne Oostenbrink noemen, die altijd snel en ongezouten mijn teksten retourneerde, die me wees op mijn verantwoordelijkheden, een logische opbouw van een betoog en wat waar hoort volgens de ongeschreven afspraken van de wetenschappelijke wereld. Dankjewel Rianne, je bent een soort schaduw-co-promotor voor me geweest. Agnies van Eeghen, 'onze' gedreven AVG-arts die al heel wat voor elkaar krijgt binnen en buiten ENCORE- dank dat ik mocht aansluiten bij het kwalitatieve onderzoek, dat heeft me inmiddels al heel wat gebracht. De

harde werkers van de kinderneurologie hebben het gezicht bepaald van mijn start binnen ENCORE, vooral dank aan Coriene, Femke, Marie-Claire en Margreet voor jullie welkom tijdens mijn eerste jaren in dit werk. ENCORE is inmiddels een respectabele denktank van fundamenteel tot klinisch onderzoek waarbij ik onder andere heb kunnen profiteren van de inbreng van mensen als Cindy Navis, Karen de Heus, Maartje Radstaake, Mariëlle Caspers, Rick van Minkelen, Shimriet Zeidler en Suzanne Pasmans.

Andere co-auteurs, meedenkers en collega's waarmee ik helaas soms meer digitaal dan in levende lijve communiceer: AnneLoes van Staa (leuk dat je aan de commissie wilt deelnemen!), Cootje Donkersloot (ja, ook echte 'clinici' horen in dit lijstje!), Coriene Catsman, Frank Verhulst (zonder dat te weten inspirator van mijn laatste stelling), Jan van de Ende, Lisbeth Utens (wat jammer dat je niet kon opponeren, maar wat fijn dat je ook nog bij ons blijft!), Badies Manai (mister GCP-himself!), Hanneke IJsselstijn, Hanneke van Helden, Marie-Christine Franken, Femke Aarsen, Francis van Veelen, Lianne Krab, Pauline Both, Caspar Loomen, Walter Taal en Yvonne Vergouwe. Belangrijke meedenkers waren ook mijn collega promovendi, zoals Luuk Stapersma, Raisa Schiller, Mireille Hermans, Annelieke Hijkoop en Chantal ten Kate.

Veel van onze grotere onderzoeksprojecten waren niet zo goed geweest zonder de bijdrage van de afdeling humane genetica van het universiteitsziekenhuis Leuven: Eric Legius (dank voor al je vriendelijke uitleg en dat je in mijn commissie wilt plaatsnemen!), Ellen Plasschaert (mijn Leuvense evenknie), Mie Jef Descheemaeker, Annick Vogels en Marleen Renard. Een speciale vermelding voor de collega's van CNL Kempenhaeghe die in Oosterhout meehelpen en denken om zorg en onderzoek rond NF1 vorm te geven: Sandra van Abeelen (mijn VOLG-maatje), Annick Laridon, Alma Weber, Eddy Gaukema, Jos Hendriksen en Katrijn Verdyck.

Ook de Nederlandse patiëntenvereniging voor neurofibromatose (NFVN) heeft een onmisbare bijdrage geleverd aan verschillende projecten van ENCORE en van dit proefschrift. Het bestuur, de leden en de voorzitter Ton Akkermans zijn erg succesvol in het ondersteunen van nieuwe initiatieven en het delen van de resultaten met de leden.

Mijn ENCORE-KJPP-collega's Jeroen, Leontine, Bram, Sabine, Gwen en Pieter. Goed dat we elkaar proberen scherp te houden om de psychologische en psychiatrische kant een plek te geven binnen het ENCORE-onderzoek.

Philip Hopman en Katinka Krijgsman, dank voor jullie werk aan de illustraties, de omslag en de vormgeving- jullie hebben me geholpen om dit boek een gezicht te geven.

Manon Hillegers en Martha Grootenhuis, dank voor jullie deelname in de promotiecommissie en voor het werk dat we zowel tijdens als na mijn promotie samen zullen doen.

Studenten hebben voor mij een flinke plek ingenomen in de afgelopen jaren, ook in het denk- en schrijfwerk. Begeleiden van en samenwerken met masterstudenten, research of klinisch, maar ook van/met PhD studenten, Gz-psychologen, schoolpsychologen en basispsychologen vind ik een van de leukste kanten van dit werk. Speciaal dank aan de meeschrijvende studenten en collega's: mijn SPOT-maatje Charlotte Bouman, Sanne Bongers, Dora Csermak, Kimberley van Noort, Eline Pols, Jay-Dee Troost, Jessica Smid, Daniela Gawehns, and my dear colleagues abroad: Alanna Jacobs and Beth Nicholson.

Ten slotte zij die mij lief zijn en zijn gebleven, ook al is dat soms niet gemakkelijk (van jullie kant, niet van de mijne;). Mijn ouders voor alles wat ze tot hun einde hebben gegeven aan mij, mijn lieve (schoon)ouders Hielke en Lidia Ploeg, andere lieve familieleden en vrienden. In het bijzonder natuurlijk mijn beide paranimfen Ron Rietman en Jannemieke van Wolferen, ook al verschillen jullie nog zo van elkaar, dit is wat jullie bindt: dank voor jullie vriendelijkheid, betrokkenheid en alle regelwerk dat jullie zomaar voor mij willen doen. En lest best, de mensen die elke dag kleur aan mijn leven geven: mijn beste vriendin, mijn klankbord en grote liefde Monique en de mooiste en liefste kinderen van de wereld: Kjeld, Sybe en Ymkje. Ik kan niet in woorden zeggen wat het betekent om jullie in mijn leven te hebben.

VIII. Curriculum vitae

André Bernard Rietman was born as the second son of Bernard Rietman (1938-2015) and Sophia Geertruida Wilhelmina van der Spek (1933-2010) on the 7th of July in 1964 in Warnsveld, the Netherlands, where he was raised as well. After primary education in Warnsveld and secondary education in Zutphen, he studied at the HBO Occupational Therapy in Amsterdam. He got his bachelor degree in 1986 and started working as an occupational therapist in adult psychiatry, child psychiatry, a private practice, and in child rehabilitation. In 1988 he started the department of occupational therapy in Curium, a center for child psychiatry in Oegstgeest. During his work as an occupational therapist he started studying psychology in the evenings (from 1992) and he obtained his master's degree (Cum laude) in 1997. In that same year, he started working as a psychologist at the 'Pedologisch Instituut' (Centre for Child studies) in The Hague).

In 1999 André completed the European graduate school for child neuropsychology at the Free University Amsterdam (Cum laude). In 2004 he was registered as a Healthcare psychologist (Gz-psycholoog). In 2008, together with pediatric neurologist Liesl Rehbock, he started the neurology outpatient clinic of Kinderhaven in Rotterdam. When ENCORE (*Expertise Center for Neurodevelopmental Disorders, Erasmus Medical Center, Rotterdam*) was started in 2010, he started working at the Erasmus Medical Centre Sophia Children's Hospital in Rotterdam, the Netherlands. First for the department of pediatric neurology, from 2015 for the department for child and adolescent psychiatry/psychology and for the department of surgery (outpatient clinic for long-term follow-up of children that had surgery early in life (CHIL)). From 2010, as part of the ENCORE-team he started the VOLG program (*Vroegtijdige Onderkenning Leer- en Gedragsproblemen*: early recognition of problems in learning and behavior), first for children with Neurofibromatosis type 1 (NF1), Tuberous Sclerosis Complex (TSC), or Angelman syndrome, later also for other syndromes within ENCORE. He was the psychologist for various trials examining the effect of medication on epilepsy, behavior, and learning of children with NF1 or TSC working together with PhD students Thijs van der Vaart, Iris Overwater and Myrthe Ottenhof. He led the SPOT-NF1 trial for Social and Psychosocial support for people with NF1 in their Teens or Twenties, together with Charlotte Bouman.

André did courses and had supervision on sensory processing, neurodevelopmental therapy, traumatic brain injury, cognitive behavioral therapy, solution focused therapy, system-oriented psychotherapy, statistics, biomedical English writing and communication, regulations in research (BROK), etc. From 1992 he teaches at several institutions, gives lectures and courses in the Netherlands and Belgium, and writes books and papers about various subjects: sensory processing, language- and learning disorders, regulation disorders, sensory-motor problems, neuropsychology, attention, ADHD, autism, parental guidance, psychopathology, and child development. He presented his research in NF1 at several national and international conferences. He supervises and supports master students in clinical work and research, starting psychologists, Healthcare (Gz-) psychologists and School psychologists in training, and PhD students.

André is the partner of Monique Ploeg, who is also the mother of their sons Kjeld (1994) and Sybe (1997) and their daughter Ymkje (2004). They live in Delft with their cats and rats.

Neurofibromatosis type 1 (NF1) is a genetic disorder leading to symptoms in the skin, the bones, and the nervous system, but also to an increased risk of having benign and malignant tumors. NF1 leads to unpredictable and variable complications and a lower quality of life. Cognitive deficits and behavioral problems are among the most common complications of NF1 in children. This thesis focuses on the behavioral phenotype including the most frequent cognitive, behavioral, emotional and social problems of NF1.