Falls, physiotherapy and training in patients with cerebellar degeneration

Ella Fonteyn

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Voor mijn ouders

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Chapter 1
Introduction

Ataxia

Ataxia derives from the Greek word ataxis, and means lack of order. Hippocrates and Galenus used it as a medical term for everything involving irregular movements, such as an irregular pulse.[1] Nowadays, the term ataxia is used to describe incoordination of voluntary movements. Cerebellar ataxia needs to be distinguished from sensory ataxia. The latter is due to loss of proprioception, generally caused by large fiber peripheral neuropathies and conditions causing dysfunction of the dorsal columns of the spinal cord. Typically, sensory ataxia worsens upon eye closure. Cerebellar ataxia is the result of dysfunction of the cerebellum and its connections. In contrast to sensory ataxia, cerebellar ataxia does not worsen markedly upon eye closure, and is often accompanied by other cerebellar signs, such as eye movement abnormalities (jerky pursuit, gaze-evoked nystagmus, dysmetric saccades) and dysarthria. Sensory and cerebellar ataxia can sometimes coexist, for example in some genetic ataxias.[2, 3]

Cerebellar ataxia can have a great impact on quality of life, mainly due to impaired dexterity, balance disturbances, and consequently falls. Furthermore, cerebellar ataxia is a challenging symptom for clinicians in daily practice, because of the extensive differential diagnosis, the lack of treatment options, the long list of potential concomitant symptoms, and the consequences of ataxia for daily life of patients.

This Introduction means to give a more general, concise and practical overview of cerebellar ataxias, mainly focussing on the clinical reasoning, but also including comments on the management of cerebellar ataxia. The focus of this chapter and thesis will be on adult-onset ataxias, i.e. not on congenital or childhood-onset ataxias (although some diseases that typically start in adulthood can start earlier in life).

Differential diagnosis and diagnostic work up of cerebellar ataxia

The causes of cerebellar ataxia are numerous. Even some of the relatively frequent causes are quite rare, which makes the diagnostic work-up of patients with ataxia rather complicated. For a focused differential diagnosis and targeted work-up, carefully history taking and looking for relevant clues during the physical examination are crucial.

Relevant information from the history

Continuous or episodic

When ataxia appears to be episodic, the differential diagnosis is very limited, and mainly includes migraine and the genetic episodic ataxias. Basilar-type migraine, familial hemiplegic migraine (FHM1) and sporadic hemiplegic migraine can cause episodic ataxia, which is most often accompanied by vertigo, dysarthria and visual disturbances, typically followed by a pounding occipital headache and

nausea, which completely resolve after some hours. Two-thirds of the patients with FMH1 have permanent cerebellar involvement, including gaze-evoked nystagmus, ataxia, and atrophy of the vermis. Some families have severe attacks with coma or prolonged hemiplegia, with full recovery.[4, 5]

There are seven genotypes of dominantly inherited episodic ataxias (EAs), of which EA1 and EA2 are most common. Onset is usually in late childhood or adolescence. Mutations can be de novo, leading to a negative family history. Depending on the mutation, patients experience episodes of ataxia lasting minutes to hours, occasionally days. There may be other accompanying features, such as vertigo or tinnitus, which sometimes predominate. Interictal findings are indicative, for example myokymia points to EA1, and nystagmus to EA2. In EA2, there may be a slowly progressive cerebellar syndrome that evolves over the years.[6]

Speed of onset and progression rate

Acute onset of cerebellar ataxia obviously suggests a stroke of the cerebellum or brainstem. Ataxia developing over hours may be due to alcohol intoxication or Wernicke's encephalopathy. Wernicke's encephalopathy, caused by vitamin B1 deficiency, is characterized by encephalopathy, oculomotor dysfunction and gait ataxia as the classic triad, and requires immediate vitamin B1 replacement. Symptoms that develop over days may be the result of Miller Fisher syndrome or postinfectious cerebellitis (which is rare in adults). Progression in weeks to months is seen in structural lesions of the cerebellum or brainstem, ataxia due to drugs, paraneoplastic cerebellar degeneration, steroid-responsive encephalopathy with antithyroid antibodies (SREAT, formerly known as Hashimoto's encephalopathy), Creutzfeldt-Jakob disease, and antiglutamic acid decarboxylase (anti-GAD)-associated cerebellar ataxia. A gradual onset and progression over years often points to a degenerative cause. There are obvious exceptions to these lists, but the message is that onset speed and progression rate clearly makes some conditions far more likely than others.

Onset at age

Particularly for the genetic ataxias, age at onset seems to be a less useful indicator. For example, some of the recessive ataxias - which were previously assumed to begin in early life - can start really late.[7] Still, an onset below 40 years of age has an increased likelihood of being genetic in origin, in comparison with an onset after that age. Multiple system atrophy (MSA) does not need to be considered before 30 years of age[8], and the fragile X tremor/ataxia syndrome (FXTAS) generally starts after 50 years of age.[9]

Family history

A genetic cause is of course evident if there is a family history of cerebellar ataxia. The mode of inheritance, suggested by the pedigree, determines which genetic mutations should be looked for. A negative history does not exclude a genetic cause. It is important not only to ask for ataxia in other family members,

but also for other movement disorders (e.g. parkinsonism is relatively common in SCA2, and chorea can be part of the SCA17 phenotype), for mental retardation and premature ovarian failure (for FXTAS), and for deafness and diabetes mellitus (for mitochondrial disorders).

General medical status

Changes in body weight and diarrhea can point towards a thyroid problem or to celiac disease. Patients with a history of malignancy may have paraneoplastic cerebellar degeneration. HIV patients may develop a cerebellar ataxia due to various reasons (opportunistic infections, primary CNS lymphoma, etc.). Autonomic problems, such as urinary incontinence or orthostatic hypotension, suggest MSA. If the patient has a history of longstanding alcohol abuse, the likely diagnosis is alcoholic cerebellar degeneration, or – if the ataxia developed over hours - Wernicke's encephalopathy due to B1 deficiency (secondary to malnutrition).

Exogenous substances

Longstanding alcohol abuse is the most common exogenous substance that causes chronic ataxia. Although alcohol is the most frequent cause of sporadic ataxias in middle-aged men, a search for other causes still needs to be considered if the alcohol abuse has not been too excessive, or if there is progression after stopping alcohol intake. Other exogenous substances that can cause ataxia include cannabis, NMDA receptor antagonists, and heavy metals such as mercury, organo-lead components and methylmercury.[10]

Various prescription drugs, such as antiepileptic drugs, amiodarone, benzodiazepines and lithium can cause ataxia, which is reversible in the majority. Chemotherapy, especially 5-fluorouracil, cytarabine and methotrexate, is associated with both reversible and permanent cerebellar ataxia, and also can lead to permanent sensory ataxia, due to peripheral neuropathy.[11, 12]

Relevant clues from the physical examination

The neurological examination should firstly confirm that there is indeed a cerebellar ataxia. Relevant other elements of the neurological examination include peripheral neuropathy, spasticity (the spastic ataxias have a limited number of underlying causes), or any other movement disorder. It is worthwhile to invest in the examination of eye movements. There could be some more 'standard' cerebellar eye movement abnormalities, such as jerky pursuit, gaze-evoked nystagmus, and dysmetric saccades. However, some other eye signs are very indicative. For example, a severe difficulty to generate saccades (sometimes referred to as oculomotor apraxia) has a limited differential diagnosis (namely that of ataxia telangiectasia, or of ataxia with oculomotor apraxia type 2). A gaze limitation in the vertical plane might suggest Niemann-Pick type C. Some dominant ataxias (e.g. SCA1) and mitochondrial disorders are accompanied by a more extensive ophthalmoplegia.

The non-neurological signs to check are skeletal abnormalities like scoliosis (e.g. Friedreich ataxia), telangiectasias (ataxia telangiectasia) and orthostatic hypotension (MSA).

Investigations

Tables 1 and 2 show possible causes of non-genetic and genetic ataxias, respectively, including associated symptoms, abnormalities on MRI imaging, and suggestions for further investigation. Not included in the table are ataxias due to traumatic brain injury, hypoxic encephalopathy, radiation, high altitude cerebral edema, and heat stroke, which are evident from the history.

The investigation of patients with cerebellar ataxia should always begin with an MRI brain scan, or a CT brain scan in acute onset ataxias. The only exception might be the patient in whom there is a known genetic ataxia with a compatible clinical presentation. If the MRI shows no structural lesion, there may be hallmarks of specific ataxia causes. (Table 1 and 2)
For the further phenotyping, electrophysiological investigations need to be considered. It is particularly useful to ascertain whether or not a peripheral neuropathy is present. Also, an ophthalmology referral is sometimes required to exclude or confirm abnormalities of the optic nerves (atrophy, edema), retinal pigmentary changes, macular dystrophy, and Kayser-Fleischer rings.

TABLE 1 Acquired and (non-genetic) degenerative causes of cerebellar ataxia [13, 14]

CAUSE	CLUES	SUGGESTIONS FOR INVESTIGATION
Structural lesions		
Stroke, MS, space occupying lesions, Chiari malformation	Focal neurological signs, headache	Investigations depend on findings on CT or MRI brain scan
Toxic		
Alcohol	Medical history, concomitant neuropathy	Liver enzymes, MCV, vitamin B1 MRI: anterior vermis atrophy
Drugs, heavy metals	Medical history	Blood level drug, stop use or exposure
Inflammatory		
Paraneoplastic cerebellar degeneration	Rapid progression, history of malignancy	Anti-neuronal antibodies, tumor screen MRI: cerebellar atrophy (later stages)
Anti-GAD ataxia	Subacute, type 1 diabetes mellitus	Anti-GAD antibodies MRI: cerebellar atrophy (later stages)
Steroid-responsive encephalopathy with antithyroid antibodies	Subacute, seizures, myoclonus, rapid response to steroids	Anti-thyroperoxidase antibodies
Gluten ataxia	Gastro-intestinal symptoms	Anti-tissue transglutaminase and anti-endomysium antibodies, bowel biopsy

CAUSE	CLUES	SUGGESTIONS FOR INVESTIGATION
(Para)infectious		
Epstein-Barr virus	Subacute, preceding infection	Serologic testing, CSF
Miller Fisher syndrome	Subacute, ophthalmoplegia, areflexia	Anti-GQ1b antibodies, EMG
HIV-related ataxia	History of HIV infection Opportunistic infections such as toxoplasmosis, PML	MRI, CSF, search for opportunistic infections
Whipple's disease	Fever, weight loss, diarrhea, abdominal pain, arthritis	PCR finding of Tropheryma whipplei in duodenal biopsy
Tabetic neurosyphilis	History of syphilis, sensory ataxia	TPHA, CSF
Metabolic		
Vitamin B1 deficiency (Wernicke's encephalopathy)	Confusion, nystagmus, ophthalmoplegia	Vitamin B1 level MRI: bilateral increased T2 signal in the thalamus, hypothalamus, mammillary bodies, periaqueductal region, fourth ventricle floor, and midline cerebellum
Vitamin E deficiency	Diarrhea	Vitamin E level, celiac screen, serum amylase
Hypothyroidism	Fatigue, weight gain, constipation	Thyroid stimulating hormone, free T4
Hypoparathyroidism	Cataract, extrapyramidal symptoms	Parathyroid hormone, calcium, phosphate CT: cerebellar and basal ganglia calcifications
Other		
Superficial siderosis	Sensorineural deafness, pyramidal signs	Audiogram, xanthochromic CSF MRI: linear hypointensity in the posterior fossa on T2-weighted gradient-recalled echo
Degenerative		
Multiple System Atrophy	Autonomic failure, parkinsonism	Autonomic testing MRI: hot cross bun sign (pontocerebellar fiber degeneration) and putaminal rim (high signal line extending laterally from slightly darkened putamen)
Idiopathic late onset cerebellar ataxia/sporadic adult-onset ataxia	Relatively pure ataxia, slow progression	MRI: cerebellar atrophy
Sporadic Creutzfeldt-Jakob disease	Rapid progression, cognitive disturbances, myoclonus, pyramidal tract signs	14-3-3 and tau protein CSF, EEG MRI: Increased signal in basal ganglia and cortex on FLAIR and diffusion-weighted MRI

TABLE 2 Some important genetic causes of cerebellar ataxia [7, 13, 14]

CAUSE	CLUES	SUGGESTIONS FOR INVESTIGATION
Dominant		
Spinocerebellar ataxias	Family history, slow progression, non-ataxia symptoms, some genotype-specific features	Mutation analysis of SCA genes, repeat expansion SCAs first MRI: cerebellar atrophy
Dentato-rubro-pallidoluysian atrophy	Family history, chorea, dementia, myoclonus, Japanese descent	Mutation analysis of ATN1 gene
Alexander disease	(Pseudo)bulbar signs, spasticity	Mutation analysis of GFAP gene MRI: tadpole sign (atrophy of the medulla and cervical cord with a preserved pontine volume
Gerstmann-Straussler syndrome	Family history, pyramidal signs, adult-onset dementia	Mutation analysis of PRNP gene
Recessive		
Autosomal recessive cerebellar ataxias (in general)	Family history, often neuropathy, systemic features	Mutation analysis of recessive genes, lysosomal enzymes, metabolic investigation, α-fetoprotein
Wilson's disease	Kayser-Fleischer rings, dystonia, parkinsonism, renal tubular acidosis, cardiomyopathy	Ceruloplasmin, serum and urine copper, liver enzymes, renal function Mutation analyses of ATP7B gene MRI: hyperintense T2 signal changes in basal ganglia
Friedreich ataxia	Age at onset 5-25 years, late onset possible. Mixed cerebellar/ sensory ataxia, areflexia, pyramidal weakness, scoliosis	Mutation analysis of FRDA gene
Ataxia telangiectasia	Age of onset 2-3 years. Oculomotor apraxia, conjunctival telangiectasias, extrapyramidal signs, predisposition to cancer. Milder variants exist	α-fetoprotein Mutation analysis of ATM gene
Ataxia with oculomotor apraxia types 1	Like ataxia telangiectasia, sensorimotor neuropathy, chorea, mental retardation	Albumin, cholesterol Mutation analysis of APTX
Ataxia with oculomotor apraxia type 2	Ataxia with oculomotor apraxia type 1, some features in lesser degree, oculomotor apraxia	Serum α-fetoprotein Mutation analysis of SETX
Autosomal recessive cerebellar ataxia (ARCA) with psychomotor retardation	Psychomotor retardation in early life, late-onset ataxia	Mutation analysis of SYT14
ARCA1	Relatively pure cerebellar syndrome	Mutation analysis of SYNE1
ARCA3	Downbeat nystagmus, lower motor neuron involvement	Mutation analysis of ANO10
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	Spasticity, severe neuropathy, onset below age 10 years	Mutation analysis of SACS
SANDO/MIRAS	Ophthalmoplegia, myoclonus, dystonia, neuropathy	Mutation analysis of POLG1 MRI: cerebellar white matter high-signal changes

CAUSE	CLUES	SUGGESTIONS FOR INVESTIGATION
Late-onset Tay-Sachs disease	Proximal muscle weakness and atrophy, behavioral problems, areflexia	Enzyme assay hexosaminidase A Mutation analysis of HEXA
Cerebrotendinous xanthomatosis	Tendon xanthomas, diarrhea, pyramidal or extrapyramidal signs, seizures, dementia, cataract	Cholestanol Bile alcohols in urine Mutation analysis of CYP27 MRI: cerebellar white matter high-signal changes
Refsum's disease	Demyelinating polyneuropathy, sensorineural deafness, retinitis pigmentosa, anosmia	Phytanic acid Mutation analysis of PHYH and PEX7
Other		
Fragile X-associated tremor/ataxia syndrome	Family history (learning disability premature ovarian failure), mostly men, action tremor, behavioral changes, autonomic dysfunction	Mutation analysis of FMR1 gene MRI: hyperintense signal changes lateral to dentate nucleus extending into middle cerebral peduncles, often generalized atrophy
Mitochondrial disorders	Family history, diabetes, deafness, multisystem involvement	Mutation analysis of mitochondrial DNA and POLG1, muscle biopsy

Heredo-degenerative ataxias

Heredo-degenerative cerebellar ataxias form an interesting group, due to their clinical and genetic heterogeneity and in light of the on-going discovering of new genes. The worldwide incidence of these ataxias is estimated to be 5.2-18.5 per 100.000 inhabitants.[15-20]

Degenerative ataxias are characterized by an impairment of gait, balance, limb coordination, speech and eye movements. A plethora of other symptoms and signs may arise, and these are sometimes very specific for one of these disorders.[21] Symptoms are progressive and eventually lead to serious deterioration of mobility, independence, and quality of life.[22, 23] A prior study found that falls occur very frequently in these patients, and that these falls often lead to injuries and a fear of falling.[24]

Many degenerative ataxias have a genetic cause. Based on the mode of inheritance or on the identified gene defect, hereditary ataxias can be categorized into autosomal dominant, autosomal recessive, X-linked, and maternally inherited disorders. This thesis focuses mainly on autosomal dominant cerebellar ataxias (ADCAs), which are currently referred to as spinocerebellar ataxias (SCAs). The prevalence in The Netherlands has been estimated at about 3 per 100,000, but is probably higher.[16]

An important non-genetic, degenerative ataxia to consider is multiple system atrophy (MSA). If no exact cause can be established, the terms Idiopathic Late Onset Ataxia (ILOCA) or Sporadic Adult-Onset Ataxia of unknown etiology (SAOA) are used.[25] These are usually relatively slow progressive and rather pure ataxias. If not, one should reconsider diagnosis.

Treatment and management of cerebellar ataxia

For only a small number of cerebellar disorders there is a specific treatment. Some specific interventions include stopping the offending substance in toxic ataxia; starting vitamin supplements in vitamin deficiencies; specific dietary recommendations in celiac disease and Refsum's disease, starting corticosteroids in patients with SREAT or ataxia associated with anti-GAD antibodies, treating the underlying tumor and starting immunomodulatory treatment in paraneoplastic cerebellar degeneration, and giving bile acid replacement in cerebrotendinous xanthomatosis. With regard to symptomatic, anti-ataxia drugs such as amantadine or riluzole, the number of well conducted studies is disappointingly low and therefore evidence to support their use in practice is lacking.[26] Drugs for the potential other disease manifestations are available, for example, to partially alleviate spasticity, nystagmus, parkinsonism, orthostatic hypotension, or urinary urgency.

However, for most patients there is no specific treatment and the aim is then to provide symptomatic relief and supportive care and to prevent further complications. Other specialist doctors that are often needed include rehabilitation specialists, clinical geneticists, and urologists.

Allied health care

Patients are often referred to allied health care interventions, which are considered as the cornerstone in further management.[27, 28] Physical therapy, speech therapy, and occupational therapy are expected to prevent secondary complications and minimize dependency in daily life in patients with ataxia. However, despite the many referrals, there is not much known about when and where to refer patients, and which training program to use. There is not much scientific evidence for the effectiveness of interventions used in allied health care, leading to a lack of evidence-based treatment guidelines and a marked heterogeneity of treatments that patients with ataxia receive.[29]

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Chapter 2

Aims and outline of the thesis

Falls are one of the major consequences of balance and gait disorders. At the time of this thesis, not much was known about the prevalence, impact and mechanisms underlying these falls in patients with cerebellar degeneration. This lack of knowledge contrasts with the large number of studies that have been conducted for other neurological conditions, such as patients with Parkinson's disease or patients with a stroke.[1-4] The first part of this thesis (**chapters 3.1** and **3.2**) describes the results of a European retrospective study and a prospective study among patients with degenerative ataxia, which aimed to obtain further insight into the incidence, characteristics and consequences of falls and near-falls in patients with degenerative cerebellar ataxia. Such details are required to design better tailored fall prevention programs.

The second part of the thesis (**chapter 4.1 - 4.3**) focuses on allied health care, and especially on training by physiotherapists in patients with cerebellar ataxia. Many patients with degenerative cerebellar ataxia are referred to physiotherapy, probably stimulated by the fact that symptomatic pharmacotherapy and curative therapies are currently unavailable. While allied health care therapies are responsible for a significant portion of the annual health care expenses in this group of patients, actual data on the quantity and quality of such interventions were lacking. **Chapter 4.1** provides a systematic review of the effectiveness of allied health care in patients with cerebellar ataxia. **Chapter 4.2** describes the results of a national questionnaire study, providing more insight into the referral patterns, utilisation, patient satisfaction and professional expertise concerning physiotherapy in patients with cerebellar degeneration.

From the systematic review described in **chapter 4.1**, it became clear that an intensive, targeted, and high-frequency training, followed by chronic, less intensive training at home or at a physiotherapist practice, might be the best training strategy in patients with cerebellar degeneration. We, therefor, chose to perform a pilot study on the effect of a gait adaptability training program in patients with cerebellar ataxia. Previous studies showed positive effects of such a training on gait and balance parameters in patients suffering from stroke, and also demonstrated an improvement of obstacle avoidance in healthy elderly.[5-7] The results of this study are described in **chapter 4.3**.

Finally, the results presented in this thesis are summarized and discussed in **chapter 5**. A summary written in Dutch is included in **chapter 6**.

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Chapter 3
Falls in cerebellar ataxias

3.1 Falls in spinocerebellar ataxias: results of the EuroSCA fall study

Ella M.R. Fonteyn, Tanja Schmitz-Hübsch, Carla C. Verstappen, Laslo Baliko, Bastiaan R. Bloem, Silvia Boesch, Lisa M. Bunn, Perrine Charles, Alexandra Dürr, Allesandro Filla, Paola Giunti, Christoph Globas, Thomas Klockgether, Bela Melegh, Massimo Pandolfo, Anna De Rosa, Ludger Schöls, Dagmar Timmann, Marten Munneke, Berry P.H. Kremer, Bart P.C. van de Warrenburg.
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Abstract

The objectives were to investigate the frequency, details and consequences of falls in patients with autosomal dominant spinocerebellar ataxias (SCAs), and to derive specific disease-related risk factors that are associated with an increased fall frequency. 228 patients with SCA1, SCA2, SCA3 or SCA6, recruited from the EuroSCA natural history study, completed a fall questionnaire that assessed the frequency, consequences, and several details of falls in the previous twelve months. Relevant disease characteristics were retrieved from the EuroSCA registry. The database of the natural history study provided the ataxia severity scores as well as the number and nature of non-ataxia symptoms. 73.6 percent of patients reported at least one fall in the preceding twelve months. There was a high rate of fall-related injuries (74 percent). Factors that were associated with a higher fall frequency included: disease duration, severity of ataxia, the presence of pyramidal symptoms, the total number of non-ataxia symptoms, and the genotype SCA3. Factors associated with a lower fall frequency were: the presence of extrapyramidal symptoms (more specifically dystonia of the lower limbs) and the genotype SCA2. The total number of non-ataxia symptoms and longer disease duration were independently associated with a higher fall frequency in a logistic regression analysis, while the presence of extrapyramidal symptoms was independently associated with a lower fall frequency. Our findings indicate that, in addition to more obvious factors that are associated with frequent falls, such as disease duration and ataxia severity, non-ataxia manifestions in SCA play a major role in the fall etiology of these patients.

Introduction

Autosomal dominant spinocerebellar ataxias (SCAs) are a group of heredo-degenerative disorders that mainly affect the cerebellum. These usually adult-onset ataxias share features of slowly progressive gait and limb ataxia, dysarthria, and abnormal oculomotor control. At present, 27 genetic loci are known to be involved in SCAs and 20 of the corresponding genes have been cloned.[1] The exact pathophysiological mechanisms are yet unresolved and there is still no curative treatment.

At present, we can only provide supportive care, which aims to prevent the functional consequences and complications of the disease. One of these major consequences is falling, of which the devastating physical and emotional corollaries have been reviewed extensively.[2-4] In a recent pilot study, we showed that 93 percent of patients with degenerative cerebellar ataxias reported one or more falls in the preceding twelve months and many suffered injuries due to these falls.[5] Because of the relatively small number of patients in that preliminary study, specific clinical or genetic characteristics that would allow fall prediction could not be extracted.

The ongoing natural history study of SCA patients as embedded in the EuroSCA collaborative project provided us with a unique opportunity to study falls in a large cohort of fully characterized SCA patients. We sought to investigate the frequency, details, and consequences of falls in SCA patients and specifically aimed to explore patient and disease characteristics that are associated with a high fall frequency. Such data allow us to understand the fall etiology in SCA and are also relevant for future interventional efforts and perhaps more tailored prevention.

Subjects and methods

Subjects

Patients were recruited from the EuroSCA natural history study, which is a European, clinically based, two-year follow-up study in 526 patients with SCA1, SCA2, SCA3 or SCA6. At the baseline visit, the ataxia disease stage was assessed, while the following scales were applied: the Scale for the Assessment and Rating of Ataxia (SARA), the inventory of non-ataxia symptoms (INAS), and the Functional Composite score.[6-8]

Ten of the seventeen EuroSCA centers participated in this fall study, which would result in a maximum sample size of 383 patients. Exclusion criteria included: complete loss of ambulation or permanent use of wheelchair, severe visual impairment, cognitive disturbances (judged to interfere with obtaining informed consent or with recalling previous fall incidents), and orthopaedic disorders that affect balance. Relevant disease characteristics per patient were retrieved from the EuroSCA registry and included age, gender, age at onset,

SCA type, and length of expanded CAG repeat. The database of the natural history study provided the baseline SARA score and INAS count.

Patients that participated in the EuroSCA natural history study, but not in this fall study, will be referred to as 'non-participants'.

Questionnaire

At the baseline visit of the EuroSCA natural history study, participants were asked to complete a modified version of a standard fall questionnaire, which we had used in our pilot study and which was previously used in studies on falls in Parkinson's disease and progressive supranuclear palsy.[5,9,10] The questionnaire was available in Dutch and English, and was translated into German and French by local investigators. The questionnaire had to be self-completed, but if necessary, patients were assisted by the local research physician.

A fall was defined as 'every event that results in you ending up on the floor (or any other lower surface) unintentionally'.[10] The questionnaire specifically addressed the first fall after disease onset, the frequency of falls within the last twelve months, fear of falling, restrictions in daily activities due to the falls, measures undertaken to prevent falling, and an estimation of the self-perceived confidence in one's own balance (0: no confidence, 100: full confidence).[11] Participants were also asked about fall-related injuries, fall circumstances and directions of falls, but only if they had indicated to have suffered a fall within the last month, in order to minimize possible recall bias. Finally, the questionnaire also contained questions concerning living circumstances, relevant past medical history, the use of walking aids, and the use of medication. Regarding the latter, only drugs considered to be psychotropic were documented; these mainly included anticholinergics, dopaminergic drugs, benzodiazepines, antidepressants, antiepileptic drugs, and antipsychotics.

Data analysis and statistics

Patients were classified as "fallers" if they reported one or more falls in the preceding twelve months covered by the questionnaire. In order to derive factors that are associated with a higher fall frequency, the study group was divided into "non-frequent fallers" and "frequent fallers" prior to data analysis. Those who reported to fall never to just once a year were classified as non-frequent fallers, those who fell at least once a month were classified as frequent fallers. The reason the put both the non-fallers and the participants with one fall into the group of 'non-frequent fallers', is that one fall in the past 12 months might be a chance occassion. For example, in previous studies, 24 percent of healthy controls also suffered one fall in a 12-month period.[10,11] We therefore found those who reported to fall at least once a month to represent a group with clinically relevant and likely disease-related falls. To assess ataxia severity we only used the SARA total score and the scores of the gait and stance items (SARA1 and

SARA2, respectively). To study the influence of non-ataxia symptoms, the INAS items were grouped into categories that reflect the various extracerebellar systems, e.g. neuropathy or pyramidal tract pathology.

To study potential selection bias, differences between participants and non-participants were tested for significance using unpaired t-tests for age, age at onset disease, disease duration, and SARA and INAS total scores. To examine possible correlations between the INAS scores and SARA total score, as well as other variables, we used bivariate correlations with Spearman's rho. Chi-square and Fisher exact tests were used for variables expressed as proportions.

To test the significance of differences between the frequent and non-frequent fallers, non-parametric testing was used, including the Mann-Whitney and Kruskal Wallis tests for numeric data and bivariate correlations with Spearman's rho for proportions. Multiple comparisons between the four different genotypes, including age, disease duration, age at onset, and SARA and INAS scores, were made using a one-way ANOVA-test. To evaluate whether any variable or a combination of variables influenced the frequency of falls, logistic regression analysis with Bonferroni correction was carried out on those variables that significantly differed between the frequent and non-frequent fallers. Odds ratios (OR), and 95% confidence intervals (CI) were calculated.

Results

From the source population of 383 patients, 234 patients agreed to participate, which corresponds to 61.6 percent. Of these 234 patients, four were excluded because they were found to be asymptomatic. The questionnaire of two further patients was incomplete. Thus, we were able to fully analyse the data from 228 patients, except for the analysis between the different genotypes for which we had to exclude two patients as their genotype could not be confirmed.

The EuroSCA registry contained some missing items and we only analysed items of the which the data were available for more than half (i.e. 115) of the participants, unless specifically stated otherwise.

Study group and baseline characteristics

Participants and non-participants were comparable with respect to gender, disease duration, ataxia severity (SARA), and total number of non-ataxia symptoms (INAS) (table 1). Participating patients were slightly older than non-participants and had a slightly higher age at the onset of disease. Also, the relative frequencies of the different genotypes in the study group did not match those in the group non-participating patients. The proportion of patients with SCA6 was significantly higher in the participant group compared to the non-participant group (table 1).

Compared to the non-participating patients, the participants with SCA1 had a smaller mean length of the expanded CAG repeat (45.4 ± 5.7 vs. 47.8 ± 5.4, p=0.031), and the participants with SCA3 had larger mean CAG repeat expansions (70.6 ± 4.6 vs. 67.9 ± 3.8, p<0.001). There were no such differences for SCA2 and SCA6.

In the group of participants, ataxia severity as expressed by SARA correlated with disease duration (r=0.525, p=0.001) and the number of non-ataxia symptoms correlated with ataxia severity (r=0.292, p<0.001).

TABLE 1 Baseline characteristics, participants vs. non-participants

RELEVANT BASELINE DETAILS	PARTICIPANTS (N = 228)	NON-PARTICIPANTS (N = 292)	P-VALUE
Age (yr)	52.4 ± 14.1	49.4 ± 14.0	0.008
Age at onset (yr)	41.9 ± 12.8	38.9 ± 13.7	0.009
Men (%)	49.6	54.1	NS
Disease duration (yr)	10.8 ± 6.1	10.3 ± 6.4	NS
SCA1 (%)	17.5	24.9	NS
SCA2 (%)	31.9	29.7	NS
SCA3 (%)	25.8	27.2	NS
SCA6 (%)	24.9	17.9	0.047
SARA1 'Gait'	4.0 ± 4.7	3.6 ± 2.3	NS
SARA2 'Stance'	2.5 ± 1.6	2.7 ± 1.7	NS
SARA total score	14.9 ± 7.6	15.8 ± 8.3	NS
INAS total score	4.1 ± 2.2	3.8 ± 2.5[a]	NS

The participants came from the actual source population of 383 patients, while for the group of non-participants we used the entire EuroSCA cohort minus those who participated.

[a] Complete documentation available for 71 subjects
NS = non-significant

Fall Questionnaire

The mean age at onset of the disease was 41.9 ± 12.8 years, and ranged from 7 to 77 years (table 1). The majority of the patients lived independently (82.6 percent). With regard to potential contributors to falls, 35.0 percent of all patients reported to use psychotropic medication. A small proportion of the study group had impaired vision (6.2 percent) and 14.3 percent had SCA-unrelated musculoskeletal pathology. Less than half of the patients were able to walk without support or walking aid (49.3 percent).

At least one fall in the preceding twelve months was reported by 73.6 percent of the patients (table 2). The majority of the patients fell once a year to once a month (57.7 percent), 12.3 percent indicated to fall once a week, and 3.5 percent experienced a fall every day.

The mean estimated interval between disease-onset and the first fall was 4.6 ± 4.8 years, but ranged from 0 to 25 years, implying that a fall had been the presenting feature in some patients (table 2). More than one-third of the patients, who had fallen within the last month, fell forwards, backwards or sideways equally frequent (37.4 percent), while 47.1 percent mostly fell in the anterior-posterior direction and 15.5 percent mostly fell sideways.

Of the patients who reported one or more falls in the past month, 73.6 percent had suffered an injury due to a fall and 22.5 percent had suffered a fracture. A fear of falling occurred in 60.3 percent of the patients, and a similar proportion avoided activities because of this fear. The mean estimation of the self-perceived confidence in one's own balance was 45.8 (for comparison, in a previous study of 82 healthy controls with a mean age of 59.4 ±14.2 years, this was 95.4 ± 9.7)5. The majority of patients reported to have taken measures to prevent falling, such as using a walking aid or avoiding activities (table 2).

TABLE 2 Results questionnaire

FALL QUESTIONNAIRE ITEMS	
Characteristics	
Living independently (%)	82.6
Living alone (%)	16.1
Psychotropic medication (%)	35.0
Antihypertensive medication (%)	27.9
Impaired vision (%)	6.2
Musculoskeletal pathology (%)	14.3
Walking without support (%)	49.3
First fall after onset disease (yr)	4.6 ± 4.8
Fall frequency	
Fallers ≤ 12 months (%)	73.6
Fall frequency (%)	
- never	26.4
- once a year	35.2
- at least every month, but not every week	22.5
- at least every week, but not every day	12.3
- every day	3.5
Consequences of falling	
Injurious fallers (%)	73.6[a]
- fracture (%)	22.5[a]
Fear of falling (%)	**60.3**
Restriction of activities (%)	**57.3**
Measures to prevent falls (%)	82.9
Troubled by near-falls (%)	54.8
Self-perceived confidence in balance (0-100)	45.8 ± 28.6

[a] Expressed as a proportion of the fallers.

Differences between frequent and non-frequent fallers

The mean disease duration of frequent fallers was longer (table 3). The group of frequent fallers contained relatively more SCA3 patients and less SCA2 patients (table 3). The severity of ataxia, including ataxia of gait (SARA1) and stance (SARA2), was significantly greater in the group of frequent fallers. The total number of non-ataxia symptoms (INAS count) was higher in the group of frequent fallers and the proportion of patients with pyramidal symptoms was larger. Contrarily, the percentage of patients with extrapyramidal symptoms was smaller (table 3). Upon further study, it became apparent that leg dystonia was particularly more common in SCA3 patients who were classified as non-frequent fallers (data not shown).

Frequent fallers reported more injurious falls and less balance confidence. They also used a walking aid or walking support more often than non-frequent fallers, and frequent fallers were less often able to go outdoors alone. Physiotherapy was given to 29.8 percent of the non-frequent fallers, compared to 18.8 percent of the frequent fallers (p=0.186).

TABLE 3 Differences between non-frequent fallers and frequent fallers

ITEM	NON-FREQUENT FALLERS (N = 141)	FREQUENT FALLERS (N = 87)	UNIVARIATE LOGISTIC REGRESSION EXP(B)	P-VALUE
Age (yr)	52.6 ± 15.1	51.7 ± 12.4	0.995	NS
Men (%)	54.3	42.5	0.633	NS
Age onset of disease (yr)	43.0 ± 13.3	39.7 ± 11.6	0.979	NS
Disease duration (yr)	9.9 ± 15.1	12.3 ± 6.3	1.067	0.001
Genotype (%)				
- SCA1	16.5	19.5	1.235	NS
- SCA2	38.1	23.0	0.490	0.020
- SCA3	18.0	36.8	2.551	0.003
- SCA6	27.3	20.7	0.700	NS
Independent living situation (%)	83.6	81.6	0.995	NS
Living alone (%)	16.4	14.9	0.990	NS
Psychotropic medication (%)	33.1	39.1	1.312	NS
Antihypertensive medication (%)	29.4	25.3	0.821	NS
Impaired vision (%)	8.5	2.8	0.311	NS
Musculoskeletal pathology (%)	12.7	16.7	1.287	NS

ITEM	NON-FREQUENT FALLERS (N = 141)	FREQUENT FALLERS (N = 87)	UNIVARIATE LOGISTIC REGRESSION EXP(B)	P-VALUE
SARA 1 'Gait'	3.4 ± 2.3	4.9 ± 7.0	1.187	0.001
SARA 2 'Stance'	2.3 ± 1.7	2.7 ± 1.4	1.145	0.038
SARA total score	14.3 ± 6.6	16.0 ± 6.4	1.032	0.012
INAS 'Impaired vibration sense' (%)	66.4	59.7	0.742	NS
INAS 'Impaired visual acuity' (%)	5.1	7.2	1.458	NS
INAS 'Pyramidal' (%)	37.5	59.5	2.480	0.002
INAS 'Neuropathy' (%)	38.7	49.4	1.566	NS
INAS 'Ophthalmoparesis' (%)	47.1	48.8	1.088	NS
INAS 'Extrapyramidal' (%)	9.5	1.2	0.232	0.020
INAS total score	3.7 ± 2.0	4.9 ± 2.4	1.299	0.001
First fall after onset disease (yr)	4.9 ± 4.8	4.3 ± 4.9	0.976	NS
Measures to prevent falls (%)	82.5	83.1	0.954	NS
Injurious fallers (%)a	61.4	83.3	1.938	0.008
Walking without support (%)	58.1	35.6	1.952	0.003
Fear of falling (%)	56.5	65.5	1.373	NS
Restriction of activities (%)	53.7	62.1	1.319	NS
Troubled by near-falls (%)	47.7	65.1	1.530	0.000
Confidence in balance (0-100)	52.5 ± 29.0	35.4 ± 25.3	0.978	0.000

[a] Expressed as a proportion of the fallers.
NS non-significant

Differences between genotypes

Relatively more SCA3, followed by SCA1, patients were classified as frequent fallers. Yet, the different SCA types were comparable with respect to disease duration, SARA1, SARA2 and SARA total scores, as well as to the INAS items 'impaired vibration sense', 'impaired visual acuity', and 'extrapyramidal symptoms' (Table 4). However, in SCA1 and SCA3, pyramidal features were much more frequent than in SCA2 and SCA6. SCA3 patients also had the highest frequency of neuropathy and ophthalmoparesis. The SCA6 patients were older, had a later age at onset, and had the lowest INAS count.

TABLE 4 Results of multiple comparisons between the four genotypes

ITEM	SCA1 (N = 40)	SCA2 (N = 72)	SCA3 (N = 59)	SCA6 (N = 57)	P-VALUE
Age (yr)	51.2 ± 11.4	48.6 ± 15.3	48.6 ± 11.8	63.0 ± 11.2	<0.001
Disease duration (yr)	10.8 ± 6.4	10.3 ± 5.6	11.3 ± 6.4	10.8 ± 6.1	NS
Age onset disease (yr)	40.5 ± 9.9	38.3 ± 12.5	37.1 ± 12.0	52.6 ± 9.7	<0.001
Frequent fallers (%)	42.5	27.4	56.1	32.1	0.006
SARA1 'Gait'	3.8 ± 2.5	3.2 ± 1.9	5.1 ± 8.5	3.9 ± 1.9	NS
SARA2 'Stance'	3.0 ± 2.1	2.5 ± 1.4	2.2 ± 1.4	2.3 ± 1.5	NS
SARA total score	16.9 ± 10.5	14.6 ± 6.7	13.8 ± 6.7	15.1 ± 6.9	NS
INAS 'Impaired vibration sense' (%)	62.2	66.2	71.7	53.7	NS
INAS 'Impaired visual acuity' (%)	8.6	7.9	4.5	2.2	NS
INAS 'Pyramidal' (%)	66.7	31.0	63.2	31.5	<0.001
INAS 'Neuropathy' (%)	35.0	46.5	60.6	23.6	<0.001
INAS 'Ophthalmoparesis' (%)	40.0	33.8	64.3	51.9	0.005
INAS 'Extrapyramidal'(%)	0	7.0	10.5	5.5	NS
INAS count	5.2 ± 2.2	4.3 ± 1.8	4.9 ± 2.4	2.4 ± 1.4	<0.001

NS non-significant

Logistic regression

The variables disease duration, genotype, SARA1, SARA2, SARA total score, INAS count, INAS 'pyramidal symptoms', and INAS 'extrapyramidal symptoms' were entered into a logistic regression model. Stepwise forward logistic regression analysis showed that disease duration and the number of non-ataxia symptoms were significantly associated with a higher fall frequency. For disease duration (per year): odds ratio 1.07, confidence interval 1.01-1.13, p=0.029; for the number of non-ataxia symptoms (per INAS count): odds ratio 1.35, confidence interval 1.12-1.63, p=0.002. The presence of extrapyramidal symptoms was significantly associated with a lower fall frequency (odds ratio 0.07, confidence interval 0.01-0.76, p=0.028).

Discussion

Falls have been studied extensively in patients with neurological diseases, such as Parkinson's disease, progressive supranuclear palsy, and neuromuscular diseases.[2-4,9-13] Little is known about falls in patients with hereditary cerebellar ataxias. In 2005, a pilot study was conducted in 42 patients with late-onset degenerative cerebellar ataxias, and the results indicated that falls are frequent and often injurious in these patients.[5] However, this study group was too small to derive specific factors that are associated with a higher fall frequency. Such data

are relevant, not only for obvious clinical purposes, but also to gain more insight into the causes of falling in these patients.

In this fall study, as part of the ongoing EuroSCA natural history study, 74 percent of the patients reported at least one fall in the past twelve months. In most patients, falls occurred in an early disease stage (often within the first two years of disease) and were even the presenting feature in 10 percent. The majority of the patients fell in the anterior-posterior direction, which corresponds to a previous study that examined trunk sway in SCA patients that demonstrated more anterior-posterior than lateral postural instability during everyday stance and walking tasks.[14]

Our study showed that falls often have major consequences for SCA patients, including (severe) injuries and avoidance of activities due to a fear of future falls. Factors that predicted a higher frequency of falls in the whole study group were disease duration, severity of ataxia, the INAS count (i.e. number of non-ataxia symptoms), the presence of pyramidal features, and the genotype SCA3. Contrary to other fall studies, psychotropic medication did not influence the frequency of falls.[12,13,15] We were not able to study the potential influence of spasmolytic drugs as the number of patients on these agents was too low. The genotype SCA2 and the presence of extrapyramidal symptoms were associated with a lower fall frequency.

The genotype SCA3 was identified to be one of the factors associated with a higher fall frequency. Indeed, frequent fallers were more common amongst SCA3 patients, while the four different genotypes were comparable with respect to disease duration and severity of ataxia. Interestingly, the total number of non-ataxia symptoms was highest in the SCA3 and SCA1 groups and pyramidal features in particular were much more frequent in these subtypes. The relevance of pyramidal features is also evident from the fact that within the SCA6 group, frequent fallers were observed to have more pyramidal tract involvement (data not shown).

In a logistic regression analysis, the disease duration and the number of non-ataxia symptoms were independently associated with a higher fall frequency. The number of non-ataxia symptoms, ataxia severity and disease duration were all interrelated, and the number of non-ataxia symptoms was also significantly different for the various genotypes. This might in part explain why INAS count and disease duration were identified by logistic regression analysis as a contributing factor, and ataxia severity was not.Given the clinical heterogeneity of the SCAs, in particular SCA3, it was not unexpected that the logistic regression analysis did not point to a certain genotype as predictive but rather to associated disease features.

The presence of extrapyramidal features was correlated with a lower fall frequency in the logistic regression analysis. Considering these extrapyramidal symptoms, of which the overall prevalence was low, particularly dystonia of the lower limbs was responsible for the significant difference between frequent

and non-frequent fallers. Leg dystonia was mostly observed in SCA3 patients within the group of non-frequent fallers, and not present in SCA1 patients, SCA6 patients, nor in the total group of frequent fallers (data not shown). Upon further analysis of the data, however, it was apparent that pyramidal features were less prevalent in those with dystonia (20 percent) than in those without dystonia (46.1 percent). So although extrapyramidal features came out as a separate factor in the logistic regression analysis, this might largely be explained by the absence of pyramidal features. The presence or absence of dystonia was not related to disease duration or age at onset.

We are not aware of any fall study in patients with primary or secondary dystonia, but it would be interesting to see whether falls are indeed less common in this movement disorder compared with other neurological diseases.

The results of our study should be interpreted in the context of several limitations. The first is the retrospective nature of this questionnaire study. This might have introduced a recall bias, with an underreporting or overestimation of falls. Still, the basic results of this study are to a large extent biologically plausible. Second, the questionnaire was not available in all languages and the local investigators had to translate the questions for the patients in some centers. That might have led to a slightly different interpretation of the various questions. Third, there was no full match between the participating and non-participating SCA patients, as there were some differences in age, age at onset, relative SCA frequencies, and CAG repeat expanion in SCA1 and SCA3. It is however difficult to speculate how these differences might have influenced our results, as sufficient matching was obtained for disease duration, ataxia severity, and total INAS count. Finally, the current EuroSCA natural history study does not include detailed neuropsychological evaluations and the potential influence of cognitive dysfunction might hence have remained unrecognized.

We conclude that falls are very common in SCA patients and that falls have major consequences for these patients. For SCA patients in general, disease duration, the severity of ataxia, the total number of non-ataxia symptoms, and the presence of pyramidal symptoms seem to predict a higher fall frequency. Patients with extensive extracerebellar pathology and, more specifically, frequent pyramidal tract involvement (such as in SCA3 and SCA1) are more prone to fall. It is yet unclear how to translate these findings to the clinical practice i.e. to the individual SCA patient. However, in the design of fall intervention trials in SCAs, which are currently initiated, these contributory factors should be taken into account.

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3.2 Prospective analysis of falls in dominant ataxias

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Abstract

In a previous retrospective study, we demonstrated that falls are common and often injurious in the dominant spinocerebellar ataxias (SCAs) and that non-ataxia features play an important role in these falls. Retrospective surveys are plagued by recall bias for presence and details of prior falls. We therefore sought to corroborate and extend these retrospective findings by means of a prospective extension of this fall study. 113 patients with SCA1, SCA2, SCA3 or SCA6, recruited from the EuroSCA natural history study, were asked to keep a fall dairy in between their annual visits to the participating centres. Additionally, patients completed a detailed questionnaire about the first three falls, to identify specific fall circumstances. Relevant disease characteristics were retrieved from the EuroSCA registry. 84.1 percent of patients reported at least one fall during a time period of 12 months. Fall-related injuries were common and their frequency increased with that of falls. The presence of non-ataxia symptoms was associated with a higher fall frequency. This study confirms that falls are a frequent and serious complication of SCA, and that the presence of non-ataxia symptoms is an important etiological factor in its occurrence.

Introduction

The autosomal dominant spinocerebellar ataxias (SCAs) are a heterogeneous group of usually adult-onset diseases. In addition to the progressive cerebellar syndrome, a broad spectrum of other neurological features can manifest.[1] As these diseases are currently untreatable, care for these patients is purely supportive and should aim at detecting and preventing functional complications as much as possible. One of the more common complications is falling. In a recent retrospective study that was part of the EuroSCA project, we found that falls were reported by almost 75 percent of patients and that these falls often led to injuries. We identified several determinants of falls, including disease duration and ataxia severity, but also the so-called non-ataxia features and in particular the presence of pyramidal signs.[2] We here wish to confirm these findings by means of a prospective fall study, which also allowed us to comment on the validity of the instruments used to examine falls.

Subjects and methods

Subjects

A total of 113 patients with SCA 1, 2, 3 or 6 recruited from the EuroSCA natural history study, were included. The remaining 416 patients within the EuroSCA study formed the group of "non-participants" and were used for comparative analyses.[3] Relevant disease characteristics, scores on the scale for the assessment and rating of ataxia (SARA) and scores on the inventory of non-ataxia symptoms (INAS) for each patient were retrieved from the EuroSCA registry.[4, 5] The SARA rates only ataxia-related symptoms, with higher score indicating worse performance (0-40). The INAS is a clinical checklist of non-ataxia symptoms. The INAS count reflects the number of non-ataxia symptoms in each patient. To determine the INAS count, the INAS is transformed into a set of 16 binary (yes/no) variables (hyperreflexia, areflexia, extensor plantar reflex, spasticity, paresis, muscle atrophy, fasciculations, myoclonus, rigidity, chorea/dyskinesia, dystonia, resting tremor, sensory symptoms, urinary dysfunction, cognitive dysfunction, and brainstem oculomotor signs). Higher scores thus indicate the presence of more non-ataxia symptoms.

The degree of mobility was derived from the questionnaires used for the retrospective part of the EuroSCA fall study.[2] Approval for this study according to local regulations was obtained in every participating centre and all patients gave informed consent for participation.

Fall diary and fall registration form

At their visit to the participating centre, patients were asked to start documenting falls and near-falls on a fall diary and to hand it in at the next visit. They were also instructed to fill in standarized fall registration forms for the first three falls or

near-falls. A near-fall was defined as 'losing your balance but managing to stay upright, for example by holding on to something'. The forms had to be self-completed, but if necessary, patients were assisted by the local research physician. In the fall diary patients had to fill in the date of the (near)-fall, the direction of falls, cause and fall-related injuries. The fall registration forms contained questions about the fall circumstances, including the time, location, assumed cause of the fall, injuries and whether assistance was needed to get up.[6, 7]

Data analysis and statistics

Analysis of the data with the Shapiro-Wilk test showed that the data were not normally distributed.

Patients were classified as 'fallers' if they reported one or more fall in the fall diary or fall registration forms. In order to derive factors that are associated with a higher fall frequency, the study group was divided into four groups, depending on their fall frequency. The reported fall frequencies were classified as 'never', 'annually', 'monthly' and 'weekly'. The reason the groups 'never' and 'annually' were not combined to one group, is that some patients reported more than one fall in a year, but not enough falls to categorize the frequency of falls as 'monthly'.

To assess ataxia severity, we only used the SARA total score and the scores of the gait and stance items. To study the influence of non-ataxia symptoms, we used the INAS count and the INAS items 'impaired vibration sense' and 'cognitive symptoms', while the other items were grouped into categories other than the existing INAS count categories, which reflected the various extracerebellar systems: 'extrapyramidal' (dystonia, rigidity, chorea), 'pyramidal' (hyperreflexia, spasticity, paresis) and 'impaired vision' (impaired visual acuity, double vision, ophthalmoparesis).[2]

To test for significance of differences between participants in this prospective fall study and non- participants, and between the patients grouped according to their fall frequency, we used the Mann-Whitney and Kruskal Wallis tests for numeric data and Chi-square and Fisher exact tests for proportions. Bivariate correlations with Spearman's rho was used to examine possible relations between fall frequency, the INAS count, total SARA score, disease duration, age, and age at the onset of disease.

Results

Study group and baseline characteristics

Baseline characteristics of the study population are summarized in table 1. Participating patients were somewhat older than non-participants and had a higher age at the onset of disease. Also, the proportion of patients with SCA6 was significantly higher in the participant group, which probably explains the slightly higher onset age in that group. 94.7 percent of the participants also participated in the retrospective study, and only 34.4 percent of these patients

were able to walk without support (table 1).

In the group of participants, ataxia severity (SARA total score) correlated with disease duration (r=0.600, p= < 0.001), but only weakly with age (r=0.242, p= 0.010) and the number of non-ataxia symptoms (INAS count; r=0.247, p= 0.049). The number of non-ataxia symptoms negatively correlated with the onset age (r= -0.384, p= 0.002) and age (r= -0.341, p= 0.006). Fall frequency was only correlated with the number of non-ataxia symptoms. (INAS count, r=0.300, p= 0.048).

TABLE 1 Baseline characteristics, participants vs. non-participants

FREQUENCY OF FALLS ITEM	ALL PARTICIPANTS (N=113)	NEVER (N=27)	ANNUALLY (N=24)	MONTHLY (N=28)	WEEKLY (N=3)	P-VALUE
Age (yr)	56.0±14.7	58.5±15.4	60.3±13.6	55.0±14.4	49.0±10.6	NS
Men (%)	49.6	63.0	41.7	57.1	66.7	NS
Disease duration (yr)	11.8±6.4	10.5±7.2	13.5±6.5	11.6±5.8	8.3±0.6	NS
Age onset disease (yr)	43.9±13.0	47.6±13.5	46.4±10.8	43.0±13.6	40.7±10.2	NS
SARA 1 'Gait'	3.7±2.1	3.6±2.8	3.7±1.8	3.4±1.5	4.3±1.5	NS
SARA 2 'Stance'	2.6±1.7	2.5±2.1	2.6±1.6	2.6±1.5	2.3±0.6	NS
SARA total score	15.6±7.7	15.3±10.2	15.6±5.5	15.0±5.9	12.7±1.2	NS
INAS 'Impaired vibration sense' (%)	53.5	62.5	59.1	59.3	50.0	NS
INAS 'Impaired vision' (%)	26.6	12.0	30.4	14.8	33.3	NS
INAS 'Cognitive symptoms' (%)	21.8	24.0	4.3	21.4	0	NS
INAS 'Pyramidal symptoms' (%)	45.0	28.0	34.8	39.3	66.7	NS
INAS 'Extrapyramidal symptoms' (%)	10.9	8.0	8.7	14.3	0	NS
INAS counta	3.8±2.4	2.4±1.5	4.0±2.0	3.6±2.5	7.5±2.1	0.040
Genotype (%)						NS
- SCA1	19.5	22.2	20.8	25.0	0	
- SCA2	25.7	29.6	20.8	17.9	33.3	
- SCA3	20.4	11.1	25.0	17.9	66.7	
- SCA6	34.5	37.0	33.3	39.3	0	
Mobility (%)b						NS
- Walking without support	34.3	50.0	36.4	25.9	0	
- Walking with the use of a walking aid	49.5	27.3	50.0	59.3	66.7	
- Walking with the assistance of others	9.5	0	9.1	14.8	33.3	
- Walking is impossible/ wheelchair	6.7	22.7	4.5	0	0	
Falls each month	0.7±0.9	0	0.3±0.1	0.9±0.4	3.9±1.5	< 0.001
Near falls each month	8.2±32.6	2.6 ±2.8	16.2± 52.4	2.8 ±6.4	10.8 ±7.5	0.045
Injurious fallers (%)	54.7	10.0	62.5	82.1	100	< 0.001

[a] Complete documentation available for 64 of all subjects and 44 subjects in which the fall frequency is calculated.
[b] Results of the retrospective EuroSCA Fall Study, available for 105 of all subjects and 74 subjects in which the fall frequency is calculated.
NS non-significant

Fall diary and registration forms

The majority of the patients (83.3 percent) completed the fall registration forms, and 85 subjects (75.2 percent) returned a fall diary. Some fall diaries did not mention the end date; in those patients, the date of the last documented fall was used as the end date. In three patients it was not possible to determine the time period of the fall diary. Some patients kept the diary for a much longer time period, resulting in a time period ranging from 1 to 44 months covered by the diaries. At least one fall was reported by 84.1 percent of the patients. In total 345 falls were reported. The average fall frequency was 0.68 falls each month. One third of the patients who had returned the fall diary could be categorized in the group 'annually', and a slightly larger group reported to fall monthly. Only 3.7 percent fell once a week, and none of the patients experienced falls every day. Near-falls were reported by 76.2 percent of the patients, with an average of 8.2 each month.

Of all 113 participants, 54.7 percent reported some kind of injury due to a (near-)fall, mainly bruises (table 1). Three times, a fracture was reported. Almost two-thirds of the patients fell in the anterior-posterior direction, without any difference between forwards or backwards. The majority of the falls occurred indoors. For each fall documented in the fall diary, a cause was noted. The majority of the fallers (74.2 %) listed loss of balance to be the causative factor, followed by tripping (27.0 %) and slipping (18 %). Other causes varied from hastiness, vertigo and changing direction (table 2).

TABLE 2 Details of each reported fall

ITEM	
Indoors (%)	69.9
Familiar environment (%)	80.3
Unexpected (%)	62.2
Direction of fall (%)	63.0
- Sideways	35.6
- Forwards	32.2
- Backwards	32.2
Assistance needed to get up (%)	28.2
Reported cause (%)	
- Loss of balance	74.2
- Tripping	27.0
- Slipping	18.0
- Dizziness	4.5
- Changing direction	7.9
- Uneven floor	5.6
- Hastiness	9.0
- Other cause	24.7

Differences between the fall frequency groups

The differences between the groups with a different fall frequency are summarized in table 1. There was a significant difference in the INAS count between the various fall frequency groups. The percentage of patients who reported injuries was correlated with increased frequency of falls. The patients who reported to fall annually, reported the highest number of near-falls. There were no other significant differences.

Discussion

This prospective analysis of falls confirms that in SCA patients falls are a frequent and serious complication. Also, the number of non-ataxia symptoms was again identified as a relevant determinant of a higher fall rate.

Contrary to our previous retrospective study, which included 228 patients, we could not corroborate that the presence of pyramidal features was the most relevant component among the non-ataxia features.[2] However, pyramidal signs showed a tendency for higher prevalence in frequent fallers (table 1). Similarly, while we previously showed that disease duration, ataxia severity and the SCA3 genotype were positively associated with a higher frequency of falls, the current data did not reveal this. The mostly likely explanation is the reduced power to pick up such effects due to the smaller sample size. In addition, the composition of the group of patients participating in the present study was slightly different, with relatively more SCA6 patients, in whom non-ataxia symptoms are not only less prevalent overall but, in contrast to SCA1, 2 or 3, do not seem to increase with disease duration or progression of ataxia.[5] As the picture arises that falls are less frequent in those with later-onset, uncomplicated disease, such as SCA6, this might have influenced the results. With respect to the relation of falls with disease duration, our previous finding of falls as one of the first symptoms of disease in a considerable number of SCA patients already pointed to the weak association with disease duration in this patient group.[2] This might be in support of the notion that factors other than ataxia contribute to falls, and also implies that assessment of falls and near falls is important for counseling of SCA patients in any disease stage.

There were some further differences between the results of the retrospective and the present prospective study. Compared to the retrospective data, more patients reported at least one fall in the fall diary (73.6 vs. 84.1 percent), but the overall fall frequency was lower. Also, in the prospective study, a lower frequency of near-falls was documented and a smaller proportion of the patients reported injuries in the fall diary. This might indicate that patients overestimate the frequency of falls and injuries retrospectively, or underreport (near-)falls and injuries in the fall diaries. Comparison of the fall diaries with the retrospective data at the individual level, which was possible for those who participated in both studies (n=107), showed that 40.3 percent of the patients documented

a lower fall frequency and 25.8 percent documented a higher fall frequency in the fall diary. Some fall diaries did not mention the end date; in those patients, the date of the last documented fall was used as the end date, but as the period actually covered by the diary might have been longer this could have led to an overestimation of falls. Secondly, some of the diaries were incomplete, in particular for near-falls. On several fall diaries, patients wrote that they experienced many near-falls each day, even up to 20, but they did not document each of them in the fall diary, causing an underestimation of the frequency of near-falls.

Although these differences and issues have not affected the main messages of the two fall studies, they do lead to questions with regard to the validity and applicability of the instruments used here to assess falls. This is particularly relevant as falls could serve as a secondary outcome in future trials, which warrants an accurate measurement of falls. The use of an automated fall telephone system would be a more preferable method for this purpose.[8]

Although not significant, the mobility data in table 1 suggest that the fall frequency goes down once the patients reach the state of wheelchair dependency or complete immobility. The patients who reported to fall about once a year in the fall diaries, reported the most near-falls (table 1). This may indicate that loss of balance leads to actual falls in the more frequent fallers, while others manage to keep their balance and have many near-falls. This latter group is important to recognize in the clinical setting as they could potentially benefit most from balance training and fall prevention programs, although this requires formal confirmation.[9]

Lastly, the fact that the majority of falls occurred indoors, is a point worth considering by rehabilitation physicians, physiotherapists, occupational therapists and caretakers.

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Chapter 4

Physiotherapy in ataxia

4.1 The effectiveness of allied health care in patients with ataxia: a systematic review

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Abstract

Many patients with cerebellar ataxia have serious disabilities in daily life, while pharmacological treatment options are absent. Therefore allied health care is considered to be important in the management of these patients. The objectives were to evaluate scientific evidence for allied health care in cerebellar ataxia, to identify effective treatment strategies, and to give recommendations for clinical practice and further research. We conducted a systematic search for clinical trials concerning allied health care in cerebellar ataxias using electronic databases of PubMed, Medline, Embase, Cinahl and Pedro, and references lists of articles, in the time period from 1980 up to and including December 2011 in English and Dutch. We identified 14 trials, of which the 4 best studies were formally of moderate methodological quality. There was a wide variation in disease entities and interventions. The combined data indicate that physical therapy may lead to an improvement of ataxia symptoms and daily life functions in patients with degenerative cerebellar ataxia (level 2), and in other diseases causing cerebellar ataxia (level 3). When added to physical therapy, occupational therapy might improve global functional status, and occupational therapy alone may diminish symptoms of depression (level 3). There are insufficient data for speech and language therapy. Therefore, despite the widespread use of allied health care interventions in cerebellar ataxia, there is a lack of good quality studies that have evaluated such interventions. We found some support for the implementation of physical therapy and occupational therapy, but more research is needed to develop recommendations for clinical practice.

Introduction

Ataxia is a neurological symptom that is characterized by loss of coordination of movements. The term cerebellar ataxia is used to indicate ataxia that is due to dysfunction of the cerebellum, which leads to disturbances in gait, balance and coordination, dexterity, eye movements, and speech. Ataxic gait is associated with falls and limitations in daily life.[1-4] Despite the known impairments in practice-dependent and adaption motor learning [1, 5-10], patients with damage of the cerebellum are capable of learning new strategies and to compensate for the deficits.[3, 5, 11]

There are many causes for cerebellar ataxia, but a challenging group are the degenerative cerebellar ataxias. These are progressive, mostly untreatable disorders and lead to serious deterioration of mobility, independence, and quality of life.[12, 13] For many patients with ataxia, regardless of the cause, there are no pharmacological treatment options. Patients are often referred for allied health care interventions, which are considered the cornerstone in further management. Physical therapy, speech therapy, and occupational therapy are expected to prevent secondary complications and minimize dependency in daily life in patients with ataxia. However, despite the common use of allied health care, there is an unclear scientific status with regard to the effectiveness of these interventions and a lack of evidence-based treatment guidelines. This obviously results in a marked heterogeneity of treatments that patients with this movement disorder receive.

As a first step towards a more evidence-based practice, we systematically evaluated the evidence for allied health care interventions in cerebellar ataxia.

Methods

Search strategy

A systematic search was performed in the electronic databases of PubMed, Medline, Embase, Cinahl and Pedro. Clinical trials were identified using a combination of the following terms and MeSH terms: cerebellar ataxia; ataxia; physiotherapy; physical therapy; training; exercise; rehabilitation; allied health care; speech therapy; language therapy; voice therapy; and occupational therapy. The selected time period was January 1st 1980 to December 31st 2011, and the articles had to be published in English or Dutch. The retrieved articles were examined for useful references.

Selection

Articles were included if they were prospective clinical trials evaluating the effectiveness of an allied health care intervention (i.e. physical therapy, speech and language therapy, or occupational therapy) in patients with cerebellar ataxia, without interfering co-morbidity. The interventions and outcome measures had to be clearly defined in the article. Studies assessing patients both with and without cerebellar ataxia were only included if individual data for the patients with cerebellar ataxia could be extracted. Case reports or series were considered if at least two different studies described the same treatment methods.

Evidence grading

The selected articles were assessed by two of the authors (EF, SK) and the findings of the studies were extracted and summarized. Both the quality of the study design and the conclusions were appraised according to the classification of the levels of evidence using the EBRO classification (table 1) of the Dutch Cochrane Centre and the Dutch Institute for Healthcare Improvement (CBO), member of the Guidelines International Network (GIN).[14] In case of disagreement, a third author (BvdW) was consulted to reach consensus.

Due to a substantial heterogeneity between the included studies concerning disease entities, treatment goals, interventions, follow-up period, and outcome measures, a meta-analysis could not be performed.

TABLE 1 The EBRO classification

CLASSIFICATION OF METHODOLOGICAL QUALITY OF INDIVIDUAL STUDIES	
A1	Systematic review of at least two independently conducted clinical studies at quality level A2.
A2	Randomized double-blind controlled studies of good methodological quality, sufficient power and consistency.
B	Comparative studies, not reaching the criteria for A2, including studies with retrospective or patient-control group study design.
C	Non-comparative study design/patient series.
D	Expert opinion.
CLASSIFICATION OF THE LEVEL OF SCIENTIFIC EVIDENCE	
1	Conclusion based on a systematic review at quality level A1 or at least two independently conducted clinical studies at quality level A2.
2	Conclusion based on a quality level A2 study or at least two independently conducted clinical studies at quality level B.
3	Conclusion based on a study at quality level B or C.
4	Conclusion based on expert opinion.

Results

An overview of the literature search is shown in figure 1. Up to 409 references per database search were found, of which 33 articles were selected. In addition, 5 articles were identified through reference lists. Two articles described the same study, and were considered as one publication.[15, 16] Of these selected 37 publications, [11] were excluded because of the pre-defined selection criteria. Four studies were excluded because of a retrospective study design[17-20], three due to possible interfering co-morbidity[21-23], and one for not describing which interventions were used.[24] One study was excluded since the effect of the intervention was only observed at baseline; the follow up period was evaluated by telephone, with no monitoring of the activities of the participants.[25] We were not able to obtain the full text of two articles.[26, 27] Of the remaining 26 studies, 3 did not involve training,

but focused solely on a purely measurable kinematic effect of single interventions, and were excluded for that reason.[28-30] Of the 13 selected case reports[31-43], only four could be paired because of similar treatment methods.[32, 35, 38, 39]

Finally, 14 studies remained, of which 7 studies with five or more subjects with cerebellar ataxia.[15, 16, 44-49] Only four studies could be classified as level B methodological quality, i.e. they included a control group instead of only using within-patient comparisons.[16, 44, 47, 49] Of these 4 studies, 3 used randomization either for the whole or for a part of the intervention[44, 47, 49] and 3 involved a blinded assessor.[16, 44, 47] A summary of the selected articles with at least five subjects is given in a supplementary table, Online Resource 1. The included studies were heterogeneous with respect to diagnosis, interventions and outcomes. The interventions focused on several cerebellar impairments and limitations in daily life, and varied in frequency, duration and types of exercises.

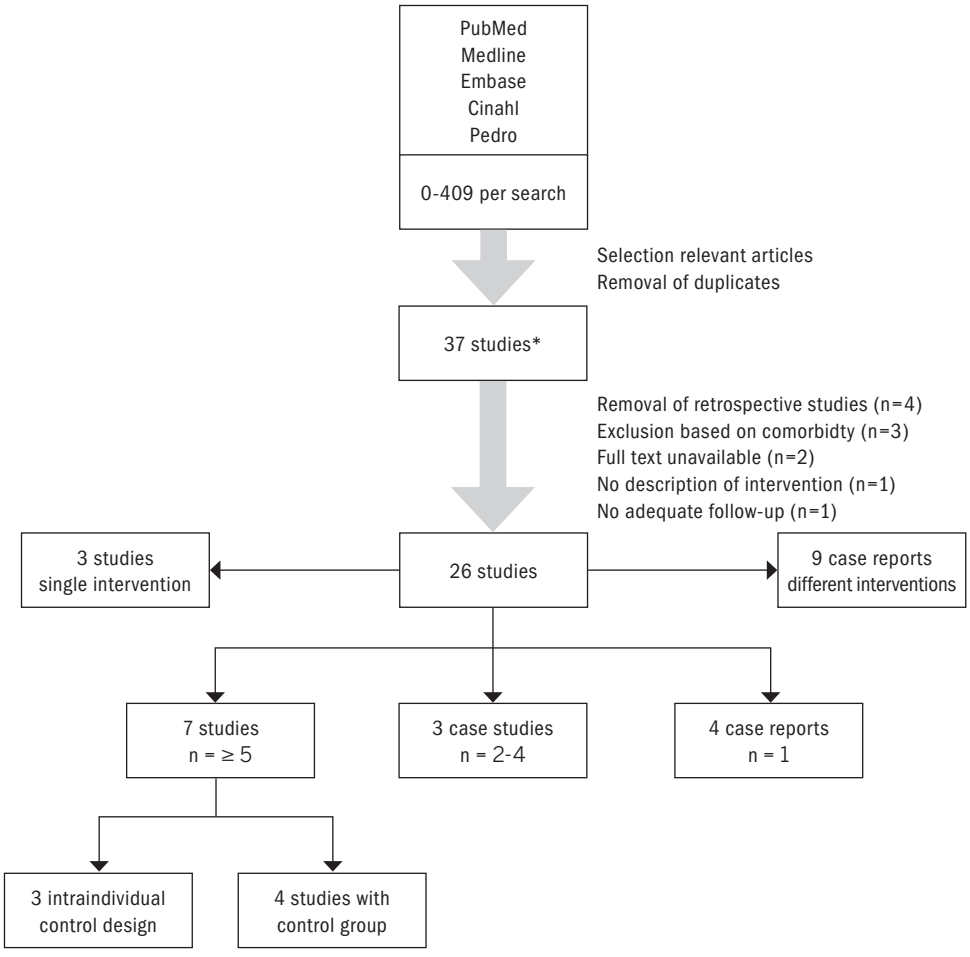

FIGURE 1 Flow diagram of literature search

Physical therapy

Thirteen studies evaluated the effects of physical therapy [15, 16, 25, 32, 35, 38, 39, 44-47, 49-52], of which two in combination with occupational therapy.[16, 47] Of these, six included at least 5 subjects.[15, 16, 25, 44-47, 49] Four of these studies could be classified as methodological quality level B (Online Resource 1).[16, 44, 47, 49] Physical therapy often focused on more than one domain, e.g. gait, balance, coordination, posture and muscle strengthening. Interventions applied consisted of conventional physical therapy exercises, computer assisted training, treadmill training, and biofeedback therapy.

Conventional physical therapy exercises

Conventional physical therapy targets at least one of the following domains: balance, gait, coordination, strength, endurance, and posture. In the majority of physical therapy interventions, aids (e.g. a cane or a walking frame) and physical therapy equipment (e.g. a balance ball, weights or a treadmill) were used.

In a study combining physical therapy with occupational therapy in 42 patients with degenerative cerebellar ataxia, physical therapy, with a focus on balance, gait, general condition, muscle strength and range of motion, led to a reduction of ataxia severity and fall frequency, and an improvement of gait speed and activities of daily living (ADL), compared to half of the patients (n=21) who received the same treatment 4 weeks later. The improvement was more prominent in trunk ataxia than in limb ataxia. Within-patient comparisons were used to analyse long-term effects, and showed that patients with mild ataxia severity experienced a more sustained improvement. In more than half of the participants, improvement of at least one item was maintained after half a year.[47] Another study in patients with degenerative cerebellar ataxia, including 10 patients with predominant effects on the cerebellum and 6 patients with predominant afferent ataxia, used coordinative training with the main goal to activate and engage control mechanisms for balance control and multi-joint coordination. Significant improvements in ADL and in gait and balance parameters, as well as a reduction of ataxia severity were seen after 4 weeks of training, compared to baseline. Training effects were more distinct for patients with intact afferent pathways. Improvements in motor and ADL performance persisted after one year and seemed to be influenced by training intensity at home.[15, 46] Training balance, gait, and muscle strength in 5 patients with chronic ataxia due to traumatic brain injury, led to an improvement in functional independence for gait.[45]

A study in 26 patients with ataxia due to multiple sclerosis (MS), combined coordination exercises, gait training, balance training, and vestibular exercises. Significant differences were found in sensory test scores, anterior balance, gait parameters, diadochokinesis, equilibrium coordination tests, and Expanded Disability Status Scale (EDSS), compared to baseline. Limb ataxia was more resistant to physical therapy than trunk ataxia. Use of Johnstone Pressure Splints in addition to exercise was of no further benefit.[44]

One study in 37 MS patients with ataxia found that physical therapy with weighting, together with occupational therapy, resulted in improvement of functional ability concerning ADL tasks, fatigue, and physical functioning, compared to patients (n=9) who did not receive any intervention. The physical therapy was focused on promoting normal posture and movement using weight bearing, damping and weighting, joint approximation and compression, and stimulating automatic equilibrium reactions using a gymnastic ball.[16]

Treadmill training

Treadmill training in two patients with ataxia due to traumatic brain injury improved gait and balance parameters.[52] Locomotor training using bodyweight support on a treadmill and over-ground walking in a patient with traumatic brain injury lead to improvement of balance, gait parameters, motor tasks and isometric trunk endurance tests.[35] In a child with severe ataxia after a cerebellar infarct, bodyweight support on a treadmill and during over-ground walking improved her walking and transfer abilities.[32]

Relaxation and biofeedback therapy

Three articles suggested a positive effect of biofeedback therapy in patients with ataxia.[38, 39, 50] In case series using electromyogram (EMG) biofeedback in three patients with ataxia due to multiple sclerosis and degenerative cerebellar ataxia, subjects were able to reduce the amount of inappropriate coactivation of muscles groups.[50] Relaxation and EMG biofeedback decreased severity of ataxic tremor in two case reports with patients with traumatic brain injury.[38, 39]

Computer-assisted training

Improved coordination of the upper limbs after training with adaptive robot therapy was suggested in a study of 8 MS patients with ataxia of the upper limbs. The training consisted of performing planar reaching movements while grasping a handle of a robotic manipulandum, which generated forces that either reduced or enhanced the curvature of the movements.[49]

Supervised sports

One study noticed that patients showed improvement of velocity and speed symmetry in pointing movements of limbs, balance and manual dexterity after climbing training. The four participants suffered from upper and lower limb ataxia due to different acquired causes.[51]

Occupational therapy

One study assessed the use of occupational therapy for cerebellar ataxia.[48] Another two evaluated its use combined with physical therapy.[16, 47] In one study, 26 patients with SCA3 were treated with occupational therapy alone, using the rehabilitative compensatory model.[53] Hamilton scores for depression improved,

but disability scores and quality of life scores remained stable. Therapy was adjusted to the needs of the patients.[48]

Occupational therapy, combined with physical therapy, including the provision of equipment and advice on ADL tasks, led to a significant improvement in speed and ability of completing ADL tasks in a study with 37 patients with ataxia due to multiple sclerosis.[16]

Intensive rehabilitation with occupational therapy combined with physical therapy was shown to be of benefit in a study of 42 patients with degenerative cerebellar ataxia. Occupational therapy focused on ADL tasks, relaxation, personal hygiene, but also on balance exercises, coordinative tasks of the upper limbs and trunk, and dual motor tasks. Positive effects on functional independence, gait, ataxia severity and falls were found, and maintained in more than half of the participants after half a year.[47]

Speech and language therapy

Only two case reports described the use of speech and language therapy, but were not included.[42, 43]

Conclusions

Table 2 contains the level of scientific evidence for the various interventions and shows the etiological category for which these interventions are applicable. We were not able to make more than two conclusions at level 2 of the EBRO classification, meaning they were based on at least two independently conducted comparative studies, but not randomized, not double-blind controlled, or with insufficient power and consistency (table 1).

TABLE 2 Summary of the level of scientific evidence for the various interventions

CONCLUSIONS	DIAGNOSIS	LEVEL OF SCIENTIFIC EVIDENCE
Physical therapy		
Conventional physical therapy		
It is plausible that physical therapy improves ataxia severity, balance, gait, fall frequency and ADL functioning. [15, 46, 47]	Degenerative cerebellar ataxia	2
Limb ataxia seems to be more resistant to physical therapy compared to trunk ataxia. [44, 47]	Degenerative cerebellar ataxia, MS	2
Long-term outcome appears to be influenced by training intensity at home. [15, 46]	Degenerative cerebellar ataxia	3
There are indications that training effects are less distinct for patients whose afferent pathways are affected. [15, 46]	Degenerative cerebellar ataxia	3

CONCLUSIONS	DIAGNOSIS	LEVEL OF SCIENTIFIC EVIDENCE
Patients with mild ataxia seem to be more likely to benefit from physical therapy combined with occupational therapy than patients with more severe ataxia. [47]	Degenerative cerebellar ataxia	3
Physical therapy may result in improvement of balance, gait, diadochokinesis and EDSS. [44]	MS	3
Use of Johnstone Pressure Splints in addition to physical therapy does not have further benefit. [44]	MS	3
Physical therapy may improve gait. [45]	TBI	3
Physical therapy with the use of weighting, together with occupational therapy, can result in improvement of functional ability, fatigue and physical functioning. [16]	MS	3
Treadmill training		
Treadmill training might improve gait and balance. [32, 35, 52]	TBI	3
Relaxation and biofeedback therapy		
EMG biofeedback may help to reduce the amount of inappropriate coactivation of muscle groups. [50]	MS, Degenerative cerebellar ataxia	3
Relaxation and EMG biofeedback might decrease severity of ataxic tremor. [38, 39]	TBI	3
Computer assisted training		
Adaptive robot therapy may improve coordination of the upper limbs. [49]	MS	3
Supervised sports		
Climbing training might help to improve pointing movements of limbs, manual dexterity and balance. [51]	Perinatal anoxic encephalopathy, TBI, stroke, metabolic encephalopathy	3
Occupational therapy		
The use of occupational therapy may diminish symptoms of depression. [48]	Degenerative cerebellar ataxia	3
Occupational therapy combined with physical therapy might improve functional status. [16]	MS	3
Occupational therapy combined with physical therapy might improve functional independence and gait and diminish ataxia severity and incidence of falls. [47]	Degenerative cerebellar ataxia	3
Speech and language therapy		
No conclusion could be made due to insufficient data.		

MS = multiple sclerosis, TBI= traumatic brain injury, EMG = electromyogram, ADLs = activities of daily functioning.

Discussion

In a Spanish study of degenerative cerebellar ataxias, the costs for health care and society were estimated to be around 24.500 USD per patient per year. The study showed that a substantial part of the direct healthcare costs was spent on allied health care.[54] Apparently, patients with functional impairments due to ataxia are often referred to allied health care workers and these referrals have become a sort of routine in the management of these patients. While an effect of such interventions is anticipated, and already experienced as such by healthcare workers and patients alike in daily practice, there is a lack of good quality clinical trials of the effects of allied health care in patients with cerebellar ataxia.

Of all allied health disciplines, the efficacy of physical therapy has been evaluated most. This is in line with other neurologic conditions, such as stroke and Parkinson's disease. Given that balance problems are a hallmark for ataxia, it was expected that for these disciplines most evidence would be found. Most of the studies identified and graded were case studies, with a moderate to poor quality of methodology. Moreover, there was a wide variation in disease entities, sample sizes, types of intervention, and outcome measures. The duration of the follow-up was usually short and variable. Based on the relatively poor quality of the studies that passed our inclusion criteria and that we have thus reviewed here, we re-examined the retrospective studies we had excluded. However, this provided no further insight, since they dealt with immediate stroke recovery (n=2), involved a non-specified intervention (n=1), or included an insufficiently characterized patient group (n=1).[17-20]

In general, therapy was tailored to the individual, which is in agreement with therapeutic principles, but makes it difficult to generalize these treatment protocols. We have here lumped the various aetiologies of cerebellar ataxias together, but we appreciate that aspects such as comorbid feature, or the intrinsic capacity to improve will differ per disease. In most trials no control intervention was used, which complicates the interpretation of whether the observed improvement was related to the specific intervention, to a more generalized and non-specific element of training, to the natural disease course, or to a placebo effect such as attention. An interesting finding in one study was that only depressive symptoms improved, without further functional benefit of the applied occupational therapy.[48] For future studies, it might be valuable to examine whether the presence of depressive symptoms influences the effectiveness of such therapies, or whether possible functional improvements are driven by a reduction of depressive symptoms due to the intervention. Similarly, the influence of cognitive disturbances, which may co-exist in many diseases that underlie ataxia, should be explored. A blinded assessor was rarely used, which may have caused bias during effects measurements. Lastly, there may be a possible publication bias, as all included studies reported a positive effect.

So, what are the practical recommendations? Physical therapy and occupational therapy are recommended in cerebellar disease, based on two level 2 conclusions for physical therapy, and the many level 3 conclusions for physical therapy and occupational therapy (table 2). However, because of the variety of, often individualized interventions and because most of the interventions were not described in full detail, it is impossible at this stage to provide a detailed guideline for such a physical therapy program The relatively better studies suggest that the program should be intensive and adjusted to the needs and limitations of the patient; that patients should be encouraged to practice at home; and that treatment should start in earlier stages of disease, since those patients seem to be more likely to benefit. Better still is to stimulate the medical community to design and conduct randomized and controlled trials that explore the effect of allied health care interventions in neurological conditions such as cerebellar ataxia. We could learn from the work done in the field of Parkinson's disease.[55]

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4.2 Physiotherapy in degenerative cerebellar ataxias: utilisation, patient satisfaction, and professional expertise

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Abstract

Physiotherapy plays an important role in the management of patients with degenerative cerebellar ataxias. However, our insight in the quantity and quality of physiotherapy prescription in this group of patients is incomplete. The purposes of this study were to investigate the utilisation of physiotherapy and patient satisfaction in patients with degenerative ataxias in the Netherlands and to examine the level of expertise and needs of physiotherapists treating ataxia patients. Questionnaires were sent to members of the Dutch association for patients with degenerative cerebellar ataxias (n=532). In addition, 181 questionnaires were sent to the physiotherapists who had recently treated the patients who responded. Eventually, 317 questionnaires from patients (60%) and 114 questionnaires from physiotherapists (63%) could be used for further analysis. Sixty-four percent of the patients were currently treated by a physiotherapist. Their median treatment duration was 5 years. 19 percent of the patients had never been referred, often despite the presence of limitations in daily activities. On the other hand, some participants without reported limitations had received physiotherapy. In general, participants were satisfied with their physiotherapist. The most reported treatment goals were improvement or maintenance of balance, general physical condition, and mobility. Physiotherapists reported lack of ataxia-specific expertise and expressed the need for education and evidence-based guidelines. Referral to and use of physiotherapy in patients with degenerative cerebellar ataxia in the Netherlands are currently inconsistent, and not in agreement with the little scientific evidence available. Referral rates are high, but referrals and actual necessity are discrepant; treatment duration is long; and ataxia-specific expertise amongst physiotherapists is insufficient. Evidence-based recommendations and specific training of physiotherapists are needed.

Introduction

Cerebellar ataxia is characterized by typical disturbances in walking, balance, dexterity, eye movements, and speech. Among the many causes, the degenerative diseases form a significant group. These disorders are progressive, incurable, and often have major consequences for mobility and quality of life.[1, 2] International prevalence estimates of degenerative cerebellar ataxias vary from 5.2 to 18.5 per 100,000 inhabitants.[3-9]

In a recent Spanish study on the costs for health care and society for degenerative cerebellar ataxias, the costs were estimated to be almost 24.500 USD per patient per year on average.[1] The study also showed that a large proportion of the direct medical expenses were explained by the use of rehabilitative interventions. This seems to be consistent with the fact that there are no pharmacological therapies for these disorders, which makes allied health care and in particular physiotherapy relevant in the management. However, it is currently unclear how many patients are actually referred for treatment and how the referred patients are being treated. Presumably, there will be much heterogeneity within the physical therapies installed. This is mainly due to the unclear scientific state of these interventions and the lack of guidelines in this area. The objective of the current study was to gain more insight into the utilization of physiotherapy for degenerative ataxias in the Netherlands. We examined both the quantity and quality of the physiotherapy, focusing on referral rates, treatment duration, expertise of the therapists, and patient satisfaction.

Methods

Study design

Questionnaires were sent to all 532 members of the Dutch association for patients with degenerative cerebellar ataxia in the Netherlands (ADCA-vereniging, www.ataxie.nl). Patients who had received treatment by a physical therapist during the previous 12 months were asked to give permission to send a second questionnaire to their physiotherapist. Subsequently, 181 questionnaires were sent to the patients' therapists. In addition to the postal questionnaires, a link to a digital version of the questionnaire for both patients and therapists was provided. The term 'physiotherapist' in this paper also entails Cesar and Mensendieck exercise therapists, who all deliver physiotherapy in The Netherlands. The questionnaires were a modified version of those previously used in comparable studies in Parkinson's disease, and have been developed by physiotherapists and neurologists.[10] Most answer options were multiple-choice, but subjects were encouraged to explain certain answers and to write additional comments. Both the questionnaires for the patients and therapists were analyzed anonymously. Approval for this study was obtained from the research ethics committee of the Radboud University Nijmegen Medical Centre, CMO Region Arnhem-Nijmegen.

Patient questionnaire

The questionnaire contained questions to gain inside in diagnosis, disease duration, falling, and any problems in mobility and daily functioning. Patients were also asked about their use of physiotherapy and whether they were satisfied therewith.

Therapist questionnaire

In this questionnaire, physiotherapists were asked about general professional and treatment characteristics, such as working experience and interest in neurological disorders and ataxia, as well as about the treatment characteristics of the specific patient referred to them, including treatment goals and duration. Therapists were asked to rank the three key treatment goals for their patient.

Analysis

Patients were classified first according their mobility in combination with their frequency of falls. This was done to evaluate the necessity for referral in relation to indications for physiotherapy. Participants who had fallen at least twice during the previous year or those who reported to use walking aids or were not able to walk, were regarded by us as having a clear indication for physiotherapy. Participants with no or mild gait difficulties (no help required), who had fallen less than two times during the previous year, were considered to have no obvious indication for physiotherapy.

Secondly, patients were classified according to the level of problems in daily life that they reported to have experienced during the previous month; no problems; mild problems; moderate problems (patient has difficulties doing simple activities without help); and (very) severe problems (patient is (often) dependent from others in daily functioning and mobility). This categorization enabled us to use the patient's perspective regarding the motives and goals for physiotherapy treatment.

Analysis of the data with the Shapiro-Wilk test showed that the data were not normally distributed. To test for differences between the different categories, non-parametric tests were used, including the Mann-Whitney and Kruskal Wallis tests for numeric data and Chi-square and Fisher exact tests for proportions. Significance level was set at <0.05.

Results

Response

Of the 532 patient questionnaires, 359 were returned (68%). Twenty-seven were sent back by respondents who were not ataxia patients, but who were on the registry because of a financial donation to the patient association. Five

questionnaires were returned blank. Of the 208 patients receiving physiotherapy in the previous year, 181 gave consent to approach their physiotherapist (87%). Completed questionnaires were returned by 116 physiotherapists (64%). Seven of the patients were excluded from further analysis, because the diagnosis was not known or not confirmed by a neurologist or clinical geneticist. One patient was excluded because of paraplegia and two patients because a different diagnosis was written on the referral letter to their physiotherapist. Therefore, 317 patient questionnaires and 114 physiotherapist questionnaires were used for final analysis. Baseline data of the patients are shown in table 1.

TABLE 1 Baseline data at the time of the questionnaire

DIAGNOSIS ITEM	ALL PATIENTS N=317 100%	SCA N=255 80.4%	ILOCA N=12 3.8%	EOCA N=7 2.2%	MSAC N=12 3.8%	OTHER DIAGNOSIS N=31 9.8%
Age (years, mean ± SD)	59.9 ± 13.5 (Range 15-89)	59.8 ± 13.1	66.3 ± 11.7	47.7 ± 16.3	68.1 ± 8.9	57.1 ± 16.1
Disease duration (years, mean ± SD)	16.2 ± 11.6 (Range 0-68)	15.4 ± 10.3	14.6 ± 14.9	29.4 ± 20.7	9.3 ± 4.8	23.4 ± 14.8
Men (%)	47.8	47.1	75.0	42.9	58.3	38.7
Asymptomatic (%)	2.8	3.5	0	0	0	0

Other diagnoses: autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), episodic ataxia type 2 (EA2), Friedreich's ataxia, and ataxia with oculomotor apraxia type 2 (AOA2)
SCA= spinocerebellar ataxia, ILOCA= idiopathic late onset cerebellar ataxia, EOCA= early onset cerebellar ataxia, MSAc= multiple system atrophy of the cerebellar type

Referral and consultation

At the time of the questionnaire, 64 percent of the patients used physiotherapy. 19 percent had never been treated by a physiotherapist. Patients who never had been treated, significantly had shorter disease duration, experienced less falls, and reported less often and less severe problems with standing, walking, changing posture, using hands in daily activities and functioning in the previous month (table 2). Most patients were referred to a physiotherapist by their general practitioner, neurologist or rehabilitation physician. However, nearly one out of ten patients visited a physiotherapist without a referral by a physician. Only 18 percent of all patients did not have a clear indication for physiotherapy. Still, 39 percent of this group currently received physiotherapy. On the contrary, 30 percent of the patients with an indication did not receive physiotherapy (data not show). Of those who never received physiotherapy treatment, 53 percent indicated that the reason for not being referred was that this had never been discussed by their physician. Patient's unwillingness to visit a physiotherapist increased with the severity of the problems experienced in the previous month, from 13 percent in patients with mild problems to 57 percent of those with

severe problems (data not shown). Reasons reported for unwillingness to visit a physiotherapist included 'no expected benefits of physiotherapy', 'doing own exercises', and 'lack of time. Of all patients who never had been referred, only 17 percent indicated that they considered physiotherapy as potentially useful, whereas 39 percent did not know whether physiotherapy could be useful.

One out of three physiotherapists reported a lack of information on the referral letter. Missing information included the precise diagnosis (69%), a treatment goal (10%), the patient's functional impairments (9%), and information about the disease (5%) (data not shown).

TABLE 2 Patient characteristics, comparing those with versus those without physiotherapy.

		PHYSIOTHERAPHY		
ITEM		TREATMENT (CURRENTLY OR IN PAST) (N=255)	NEVER BEEN TREATED WITH (N=60)	P-VALUE
Standing (%)	- No problems	9.4	34.5	<0.001
	- Mild problems (no help required)	38.6	37.9	
	- Moderate problems (some help required)	26.0	17.2	
	- Severe problems	26.0	10.3	
Walking (%)	- No problems	3.1	27.6	<0.001
	- Mild problems	22.4	41.4	
	- Walking aid needed	48.0	20.7	
	- Not able to walk	26.4	10.3	
Changing posture (%)	- No problems	3.5	20.7	<0.001
	- Mild problems	46.9	53.4	
	- Moderate problems (some help required)	31.9	19.0	
	- Severe problems	17.7	6.9	
Using hands with daily activities (%)	- No problems	24.4	48.3	0.002
	- Mild problems	48.4	38.3	
	- Moderate problems (some help required)	17.3	8.3	
	- Severe problems	9.8	5.0	
Fall frequency previous year (%)	- No falls	22.1	27.1	0.013
	- One fall	14.9	28.8	
	- More than one fall	63.1	44.1	
Functioning previous month (%)	- No problems	2.0	25.4	<0.001
	- Mild problems	39.3	47.5	
	- Moderate problems	27.0	15.3	
	- Severe problems	15.5	6.8	
	- Very severe problems	16.3	5.1	
No clear indication for physiotherapy (%)	No or mild walking problems and less than 2 falls.	54.4	45.6	<0.001
Indication for physiotherapy (%)	More than 1 fall, or walking with aid.	87.1	12.9	<0.001

Treatment characteristics

The physiotherapy was mainly provided in the therapist's clinic (table 3). Of all patients who had ever been treated, 19 percent received group treatment. Median treatment duration was 60 months (inter-quartile range (IQR) 18 to 96) for all patients being currently treated, with a median frequency of 1 session (IQR 0.8 to 2) per week. Treatment duration positively correlated with the severity of problems patients experienced in daily life within the previous month (table 3). The five main goals for treatment were the same for patients as for physiotherapists, namely improvement or maintenance of balance; general physical condition; improvement of gait; muscle strength; and self confidence (table 3). Despite the fact that patients reported falls and disabilities on the items 'stance', 'gait', 'changing posture', and 'using hands in daily activities', these items often were not selected as a treatment goal.

Treatment mainly consisted of active exercises for improving gait, balance, muscle strength, mobility, and cardiovascular fitness. The majority (88%) of the therapists used devices and tools, mainly fitness equipment. Six therapists used hydrotherapy. Therapy was evaluated with the use of measurement tools by 67 percent of the therapists treating patients functioning at higher level, and by 45 percent of the therapists treating patients functioning at lower level. Tools most often used for patients functioning at higher levels were the (Dutch) Patient Specific Complaints Test (PSK)[11] (39%), the 6-Minute Walk test (37%), and the Berg Balance Scale (26%). 29 percent of the therapists used the 10-Meter Walking Test, the Berg Balance Scale, and own tests to evaluate treatment of patients functioning at lower levels. Only one out of ten used an ataxia-specific tool, namely the Scale for the Assessment and Rating of Ataxia (SARA).[12]

A third of the therapists reported that the problem targeted by the therapy had improved during the treatment period, while 30 percent reported deterioration. Comparison of the answers of the physiotherapist with those of the patient showed that 18 percent of the therapists reported a more negative effect, while 23 percent reported a better result than the patient did. Of the patients who had reported improvement, 74 percent experienced an improvement on the long term, ranging from months to a still ongoing effect. Statistical analysis showed no correlation between treatment frequency and the reported effect. Table 3 shows the reported changes in symptoms categorized according to the functional problems in the previous month, as indicated by the patient.

On the question how much therapy was still needed for their patient, most therapists answered 'chronically', with therapy on a weekly basis.

TABLE 3 Treatment characteristics and categorization according to functioning previous month.

FUNCTIONING PREVIOUS MONTH ITEM	NO PROBLEMS (N =20)	MILD PROBLEMS (N =132)	MODERATE PROBLEMS (N=77)	(VERY) SEVERE PROBLEMS (N=87)	P-VALUE
Physiotherapy treatment ever (%)	25.0	77.7	88.5	92.0	<0.001
Physiotherapy at present (%)	25.0	57.3	69.2	79.1	<0.001
Treatment location (%)	n=4	n=101	n=68	n=78	
- Therapist's practice	50	65.5	61.6	37.5	0.001
- Hospital	0	11.0	12.7	0.9	NS
- Nursing home	0	2.0	1.5	21.0	<0.001
- Rehabilitation centre	0	14.4	10.7	9.6	NS
- Patient's home	0	4.4	12.3	26.5	<0.001
- Other	50	2.8	1.2	4.5	<0.001
Treatment duration (months, median, interquartile range)	9 (NA)	36 (12 - 72)	48 (12 - 105)	72 (48 - 132)	<0.001
Patient's goal (%)*					
- Balance	100	78.2	72.1	53.2	0.002
- Transfers	0	8.9	13.2	23.4	0.040
- Contractures	0	7.9	20.6	23.4	0.020
Treatment in line with patient's goal (%)					0.001
- No	0	1	8.8	8.0	
- Yes	100	84.8	66.2	54.7	
- Partially	0	14.1	25.0	37.3	
Something lacking in treatment (%)	25	10.7	26.0	17.4	0.034
Change of symptoms (%)					0.001
- Deterioration	0	17.7	32.8	45.3	
- Stable	25	34.4	37.3	32.0	
- Improvement	75	29.2	22.4	10.7	
- Not known	0	18.8	7.5	12.0	
If improvement, long term diminishing of symptoms (%)	100	76	71.4	57.1	NS
Change of physiotherapist after dissatisfaction (%)	0	17.2	16.7	18.9	NS
Satisfaction score (0-10, mean ± SD)	7.8 ± 0.5	7.9 ± 1.2	7.2 ± 2.0	7.4 ± 1.9	NS

* Only significant differences are shown. Other goals were improvement and maintenance of: physical condition, self confidence, muscle strength, getting up, stance, walking, walking stairs, reaching, writing, posture, moving objects, use of aids, self-reliance and turning while standing, pain reduction, and other goals

NS = non-significant

NA = not applicable

Significance level $p<0.05$

Patient satisfaction

Nearly all patients reported that the treatment was partially or totally in accordance with their goals. The mean satisfaction score was 7.6 (SD 1.7) on a 1 to 10 scale. Patients with subjective improvement gave a significantly better satisfaction score (8.2, SD 1.2) than those whose problems did not improve (7.4, SD 1.7) or those who did not know whether their symptoms had changed (7.1, SD 2.1). Seventeen percent reported that they were missing something in their treatment. Five percent of the patients missed specific knowledge or specific treatment by their physiotherapist concerning their disease. A change of therapist due to dissatisfaction was made by 17 percent of all patients ever being treated by a physiotherapist. The main reasons for switching were the same as the missing items reported above. Two percent of the patients switched because they were hoping to achieve more with the guidance of another therapist.

Professional expertise

95.6 percent of the responding therapists were physiotherapists, the remaining 4.4 percent were Cesar and Mensendieck exercise therapists. Median working experience of the physiotherapists was 13 years (IQR 5 to 24.3). Of all therapists, 81 percent were interested in ataxia, but only 11 percent of all therapists considered themselves as having expertise in treating patients with ataxia. Training in neurology, which could be a post-graduate program or a course, had been attended by 36 percent, but only 2 percent had been trained in ataxia. The median number of ataxia patients treated by each therapist during the previous year was 2 (IQR 1 to 3), varying from 1 to 20. Therapists estimated the median needed number of patients to treat to become an ataxia expert 10 (IQR 6 to 20). On the question who should treat patients with ataxia, half of the physiotherapists answered ‘all therapists’, while the other half answered ‘specialized therapists’. Two-third of the physiotherapists reported a need for guidelines for treatment of patients with ataxia. Also information about the disease (49%), education (39%), and consultation with the referrer (23%) were desired.

Discussion

This study demonstrates high physiotherapy referral rates in patients with degenerative cerebellar ataxia and generally long treatment duration in The Netherlands. This is comparable to studies in patients with Parkinson’s disease (PD).[10, 13] There might be an inclusion bias, since the patients were members of an association for patients with degenerative cerebellar ataxia in the Netherlands, and perhaps more motivated to be referred and to be trained by a physiotherapist. Despite that, this study shows that patients with relevant functional problems often do not use physiotherapy (30%). This could be important, since there is no known pharmacological treatment and patients may benefit from balance training and from learning compensatory strategies.[14, 15]

In the Netherlands, neurologists are responsible for most of referrals to physiotherapists in PD patients.[10] In our survey, general practitioners and rehabilitation physicians were responsible for as many referrals as the neurologists. More than half of the patients who had never been referred reported that physiotherapy had not been discussed by their physician. It is possible that physicians are insufficiently aware of the possible benefit of physiotherapy or there might be a lack of time to screen for relevant indications. There was also a group of patients who declined referral to a physiotherapist. Surprisingly, the proportion not wanting to be referred was relatively larger when patients experienced more disabilities, up to 57 percent. This might be due to mobility problems or a fear to go outside, refraining patients from travelling to a physiotherapist. However, it could also be the case that patients and caregivers are not aware of the possible benefits of physiotherapy even in the later stages. On the other hand, 25 percent of the patients who did not experience any problems in their functioning in the previous month, and 57 percent of the patients with mild functional problems were currently receiving physiotherapy (table 3). It might be that these patients expect too much in terms of improvement or prevention of further decline. Patients who did not experience improvement of problems were less satisfied (table 3).

Importantly, despite the specific functional impairments patients had reported on several domains, these items often were not selected as a goal for treatment. The focus of treatment goals patients had selected shifted from 'balance' in patients with no or mild functional problems to 'transfers' and 'prevention and treatment of contractures' in more advanced disease stages (table 3). Furthermore, the physiotherapists chose more training goals than their patients, but did include the goals selected by the patient. Taking these findings into account, better pre-treatment discussions between patient and therapist may lead to a more targeted and relevant way of training and an improvement of patient satisfaction.

Both patients and physiotherapists reported lack of knowledge and expertise of the therapists regarding treatment of patients with cerebellar ataxia. This is probably the consequence of the relatively low incidence of patients with degenerative cerebellar ataxia and lack of scientific evidence for physiotherapy in this group of patients.[15] Consequently, educational programs are rare. Physiotherapists reported to have been treating a median of 2 patients with ataxia in the previous year. Physiotherapists used measurement instruments not designed for patients with ataxia to evaluate the training effect. Moreover, physiotherapists and patients should be aware that ataxia is often progressive. Focusing on improvement only might therefore be counterproductive and demotivating. Physiotherapists indicated a need for education and evidence-based guidelines and often missed some information about diagnosis and treatment restrictions at referral.

Despite the inconsistency between actual treatment and treatment goals reported by the patient, and the fact that patients missed ataxia-specific

expertise of their therapist, the patient-physiotherapist relationship in general seemed to be good. Most patients were satisfied with their therapists, and 50 percent reported the same effect of the treatment as their therapist.

Several physiotherapists reported that it might be useful to refer a patient to a specialized physiotherapist or specialized allied health care team first in order to come to a suitable treatment plan, taken over by general physiotherapists or other allied health care therapists. Furthermore, the majority of the therapists reported that chronic treatment on a weekly basis is needed for their patients. This is in contrast to what is starting to emerge from recent studies. It might be more effective to start an intensive, high frequency training program first, followed by chronic, less intensive and low-frequency training at home or at the physiotherapist's practice. Such a program has been shown effective in patients with degenerative cerebellar ataxias.[14, 16] Both short-term intensive and more long-term training regimes have been shown to be safe, feasible and effective in other neurological disorders, but more research addressing the best training protocols is warranted.[17-19]

In the Netherlands, community care for patients with PD has been implemented first by developing evidence-based guidelines, followed by training of a selected number of health professionals who are collaborating in community networks, and lastly by referral of patients to these trained therapists.[20] This improved organization of care makes it easier for both patients and physicians to select the most appropriate therapist to refer to, improves quality of care, and reduces societal costs.[21] This could be the blueprint for patients with other movement disorders such as ataxia. Future research, in particular randomized clinical trials of physiotherapy in patients with degenerative ataxia, is necessary to develop evidence-based guidelines.

Conclusions

Referral to and use of physiotherapy in patients with degenerative cerebellar ataxia is currently inconsistent, and not in line with the sparse literature available. In the Netherlands, referral rates are high and referrals are insufficiently targeted. Moreover, treatment volumes per physiotherapist are low, physiotherapists have insufficient ataxia-specific expertise, and treatment duration is long. To improve care for this group of patients, the development of evidence-based physiotherapy guidelines for ataxia and community care networks of specifically trained physiotherapists is advised.

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4.3 Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration

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Abstract

Balance and gait problems in patients with cerebellar degeneration lead to reduced mobility, loss of independence, and frequent falls. It is currently unclear, however, whether balance and gait capacities can be improved by training in this group of patients. Therefore, the aim of this study was to examine the effects of gait adaptability training on obstacle avoidance and dynamic stability during adaptive gait. Ten patients with degenerative cerebellar ataxia received 10 protocolized gait adaptability training sessions of 1 hour each during 5 weeks. Training was performed on a treadmill with visual stepping targets and obstacles projected on the belt's surface. As the primary outcome, we used an obstacle avoidance task while walking on a treadmill. We determined avoidance success rates, as well as dynamic stability during the avoidance manoeuvre. Clinical ratings included the Scale for the Assessment of Ataxia (SARA), 10 meter walking test, Timed Up-and-Go Test, Berg Balance Scale, and the obstacle subtask of the Emory Functional Ambulation Profile (EFAP). Following the intervention, success rates on the obstacle avoidance task had significantly improved compared to pre-intervention. For successful avoidance, participants allowed themselves smaller stability margins in the sagittal plane in the (shortened) pre-crossing step. However, in the subsequent steps they returned to baseline stability values more effectively than before training. SARA scores and the EFAP obstacle subtask improved significantly as well. This pilot study provides preliminary evidence of a beneficial effect of gait adaptability training on obstacle avoidance capacity and dynamic stability in patients with cerebellar degeneration.

Introduction

Degenerative cerebellar ataxias are characterized by progressive disturbances in coordination, balance, and gait. Patients show an increased postural sway during stance and walking, which is omnidirectional, but greatest in anterior-posterior direction.[1, 2] Safe ambulation requires the ability to make gait adjustments dependent on environmental demands, such as stepping over uneven tiles. These step adjustments require a longer single leg stance phase. During avoidance of obstacles however, lateral instability is reported to be higher in ataxia patients due to a longer single-leg phase and simultaneous counter phase trunk movements, which are essential for obstacle crossing.[2, 3] All these factors contribute to a high risk of falling, with an incidence of falls up to 93% per year in patients with cerebellar degeneration, often accompanied with injuries and limitations in activities of daily living.[4]

There are no pharmacologic treatments available at this moment that can provide sufficient symptomatic relief. As a result, physiotherapeutic interventions play an important role in the management of degenerative cerebellar ataxias, with improvements of balance, physical condition, and gait as main training goals.[5] As the cerebellum functions as a primary site for adaptation of limb movements and dynamic regulation of balance, and cerebellar patients are also known to have deficits in motor learning[6-8], the potential effectiveness of balance and gait training can be questioned. However, there is evidence of adaptation, functional motor retraining, and motor learning after cerebellar damage.[9-11] In addition, other studies suggest potential beneficial effects of physiotherapeutic interventions on balance, gait, upper limb functioning, and ataxia severity.[5]

Since adjustment of gait patterns to the variable requirements of the environment is essential in daily life, gait adaptability training might be useful in improving walking and avoiding falls. This training modality has been reported to improve obstacle avoidance abilities and to reduce fall rates in healthy elderly. It was also found to ameliorate walking speed, step adjustments and balance in patients with stroke.[12-15] The aim of this study was to examine the effects of gait adaptability training on an instrumented treadmill with visual cues on obstacle avoidance and dynamic stability in patients with degenerative cerebellar ataxia. We hypothesized that training would improve the participants' ability to avoid sudden (physical) obstacles during walking on a treadmill, as well as dynamic stability during the obstacle crossing steps. We also expected these improvements to translate to better performance on a clinical overground walking test involving obstacle avoidance.

Methods

Subjects

We recruited ten male patients (age 61.4 ± 5.7 years, disease duration 8.5 ± 7.3 years) from the Department of Neurology of the Radboud University Nijmegen Medical Centre, seven diagnosed with Sporadic Adult-Onset Ataxia

(SAOA), two patients with spinocerebellar ataxia type 6 (SCA6), and one with spinocerebellar ataxia type 3 (SCA3). Patients were included if they were diagnosed with degenerative cerebellar ataxia and no other causes for their symptoms were found. Exclusion criteria were the use of walking aids, presence of visual impairments, other disorders influencing walking, interfering cognitive impairments, and the use of medication which may influence balance, walking or cognition. Inclusion and exclusion criteria were re-checked during an intake visit by means of a standardized medical history and neurological examination. At this intake visit, participants also completed a familiarization session with the obstacle avoidance task.

Participants did not receive other training aimed at improvement of balance or gait during the study period. All participants gave written informed consent and approval was obtained from the local medical ethics committee.

Intervention

The participants received ten protocolised training sessions of one hour each over a period of five weeks, which were supervised by the same physical therapist (JDB). Training was performed on a treadmill instrumented to project visual cues on the belt, such as obstacles and stepping targets (C-mill, Forcelink BV, Culemborg, The Netherlands)[16] (figure 1). The embedded force platform provided detection and feedback of several gait parameters, which were also used to adjust the timing of visual context to participant's gait.[17] Each training session consisted of 6 blocks of gait adaptability exercises (see appendix I). During training, participants walked at a comfortable speed (as assessed in training sessions 1, 2, and 6), without using the handrails. The level of difficulty was adapted to the participant's abilities and was gradually increased to keep the training challenging.

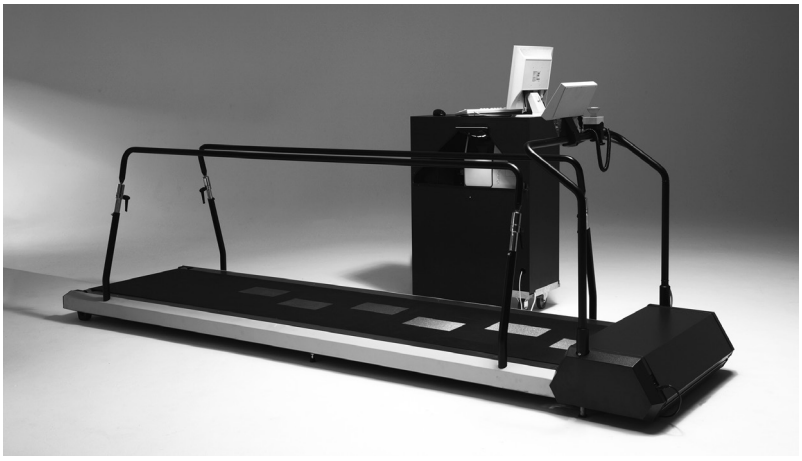

FIGURE 1 The C-mill

Pre- and post-intervention measurements

To evaluate the effects of training, the outcome measures were assessed a week before the first training (pre-intervention) and one week after the last training (post-intervention). Participants performed a standardized instrumented obstacle avoidance task while walking on a treadmill [12], and several clinical tests were done (see below).

The obstacle avoidance task involved 30 obstacles (during two series of 15 trials), while walking on a treadmill (width 1.25m [w]) at a fixed velocity of 2 or 3 km/hr, depending on the participant's abilities. A wooden obstacle (40 cm [l] × 30 cm [w] × 1.5 cm [h]) was held by an electromagnet, just above the walking surface in front of the non-dominant foot at a distance of approximately 10 cm from the most anterior position reached by the toes. Reflective markers attached to the feet, legs and trunk were recorded by a 6-camera 3D motion analysis system (Vicon, Oxford Metrics, London, UK) and were processed in real time. Based on the timing of heel strikes, a computer program (Matlab, version 2011a, The Math Works Inc., Natick) triggered the obstacle to be released at different, pre-set moments in the step cycle, which were unpredictable for the participants. Contact with the obstacle, stepping to the side, or holding on to the safety bar were defined as a failure to avoid the obstacle. Participants wore a safety harness attached to the ceiling, and their own comfortable low-heeled shoes.

The clinical tests used were the Scale for the Assessment of Ataxia (SARA)[18], the 10 meter walking test (10MWT, comfortable and fast speed)[19], the Timed Up-and-Go Test (TUG)[20], the Berg Balance Scale (BBS)[21], and the obstacle subtask of the Emory Functional Ambulation Profile (EFAP)[22]. To assess participants' level of confidence in balance, we used the short version of the Activities Specific Balance Scale (ABC).[23] Participants had to indicate on a questionnaire whether they had experienced falls in the six weeks prior to the pre-intervention and prior to the post-intervention measurements. Another purpose designed questionnaire was used to evaluate their experiences with the training.

Data analysis

Obstacle avoidance scores were noted during the experiment and verified post hoc based on video recordings and 3D marker data. To determine the difficulty level, for each trial the available response time (ART) was calculated, defined as the time span between the instant of obstacle release, and the moment when the toes would have passed the front of the obstacle if no alteration of the stride had been made. The ART was calculated by extrapolating the walking pattern of the previous steps. Trials in which the ART was too short (<0.15 s; virtually impossible to succeed), or too long (>0.75s; hardly any gait adjustment required), were excluded from further analysis.24 Obstacle avoidance success rates were calculated as the percentage of successful trials of the included trials. Step width and centre of mass excursions (CoM) were extracted from the 3D-marker data.

Step width was defined as the distance between the malleolus markers of each foot, corrected for the marker diameter. In addition, the extrapolated centre of mass (XCoM) was calculated, which corrects the centre of mass for its velocity [25]. The margin of stability (MoS) was defined as the distance between the XCoM and the edge of the base of support at foot contact.[25] The MoS was used as a measure for dynamic stability. As a measure of body sway, the peak-to-peak excursions of the XCoM in mediolateral direction were calculated.

Obstacle avoidance can be accomplished in two ways: 1) by a long step strategy, in which the step is lengthened to cross the obstacle in one go, or 2) by a short step strategy, where the step in front of the obstacle is shortened before crossing it with the ipsilateral foot. Both strategies were analysed separately regarding dynamic stability. Dynamic stability[25] was assessed in the anterior-posterior and lateral direction for the two steps prior to obstacle presentation (control steps), the shortened step in front of the obstacle (short step strategy), the steps during obstacle crossing, and the three (short step strategy) or five (long step strategy) subsequent steps. The patient specific reference MoS was determined as the average MoS of the two control steps in all trials, minus twice the standard deviation. The percentage of steps within these reference values was determined.

Statistical analysis

Outcome measures were compared between pre- and post-intervention using the Paired Sample T-Test or the Wilcoxon Signed-Rank Test, depending on whether the data were normally distributed or not (Shapiro-Wilk test). Dynamic stability was analysed using repeated measures ANOVA with step and measurement time (pre- or post-intervention) as within subject factors, with post hoc Paired Sample T-Tests. Significance level was set at $p < 0.05$, with adjusted p values ($p<0.01$) for post-hoc tests to account for multiple testing.

Results

All patients completed the training and no adverse advents occurred.

Obstacle avoidance task and dynamic stability

The level of difficulty of the obstacle avoidance task, as expressed by the average ART, did not differ between pre- and post-intervention (0.469 s vs. 0.473 s respectively, $p=0.348$). Average success rates on the obstacle avoidance task on the treadmill significantly increased from 78.5 % before training to 94.8 % after training (table 1). Participants most frequently used a short step strategy to cross obstacles, and the preference for this strategy further increased after training (76.7 vs. 63.0% before training, $p=0.003$).

In this task, dynamic stability in the anterior-posterior direction differed between steps ($F_{7,63}=29.904$, $p<0.001$). The shortened step in front of the obstacle resulted in reduced dynamic stability compared to the control steps (25.6 vs 98.8% of MoS within reference values, $p<0.001$). The deviation of MoS values from reference did not fully restore in the subsequent 5 steps (all p values <0.01).

The effects of training on dynamic stability also differed between steps (time x step; $F_{7,63}=4.813$, $p<0.001$). Following the intervention, in the shortened pre-crossing step the participants tended to allow even greater deviation from their reference dynamic stability values in order to successfully avoid the obstacle (8.9% post-intervention vs 25.6% pre-intervention, $p=0.087$). However, they more effectively restored their MoS to reference values in the subsequent steps (figure 2.a), which already began in the crossing phase (from 24.2% to 60.4% of MoS values within reference values, $p=0.004$). Dynamic stability in the lateral direction was less affected by the obstacle, and did not demonstrate effects due to training ($F_{7,63}=1.262$, $p=0.284$) (figure 2.b). No significant changes were observed in dynamic stability during the long step strategy, but it must be mentioned that only 7 participants performed this strategy at both measurements and in a very limited number of trials. The maximum step width and peak-to-peak sway did not change after training.

TABLE 1 Results of the obstacle avoidance task and clinical tests

ITEM	PRE-INTERVENTION MEAN ± SD	POST-INTERVENTION MEAN ± SD	P-VALUE
Success rate OAT (% of trials)	78.5 ± 16.8	94.8 ± 5.4	0.019
SARA (pts)	8.7 ± 2.8	8.3 ± 2.8	0.011
BBS (pts)	50.9 ± 4.2	51.2 ± 4.3	NS
TUG (s)	9.8 ± 1.7	9.6 ± 0.8	NS
10MWT comfortable speed (s)	8.1 ± 0.9	7.8 ± 0.8	NS
10MWT fast (s)	6.4 ± 0.6	6.3 ± 0.8	NS
EFAP – obstacle subtask (s)	12.8 ± 1.4	11.8 ± 0.9	0.004
ABC (%)	45.5	47.7	NS
Falls (n)	0.8 ± 1.0	0.4 ± 0.7	NS

NS = non-significant
OAT = obstacle avoidance task on treadmill
SARA = Scale for the Assessment of Ataxia
BBS = Berg Balance Scale
TUG = Timed Up-and-Go Test
10MWT = 10 meter walking test
EFAP = Emory Functional Ambulation Profile, obstacle subtask
ABC = 6-item Activities-specific Balance Confidence scale

Clinical tests and questionnaires

The results of the clinical balance and gait tests are summarized in table 1. After the intervention, the SARA scores and the EFAP-obstacle subtask score had improved. No significant improvements in the other clinical tests were found (table 1). The average SARA total score decreased from 8.7 to 8.3 (table 1). No significant differences for each subtask of the SARA score were found, but the heel-shin slide subtask improved most frequently (in four patients). The average time to complete the EFAP-obstacle subtask had decreased from 12.8 to 11.8 seconds.

Although participants appreciated the training and reported to feel more confident in daily life during evaluation, no significant changes in balance confidence (ABC) were found. Fewer falls were reported after the intervention, but this was not statistically significant.

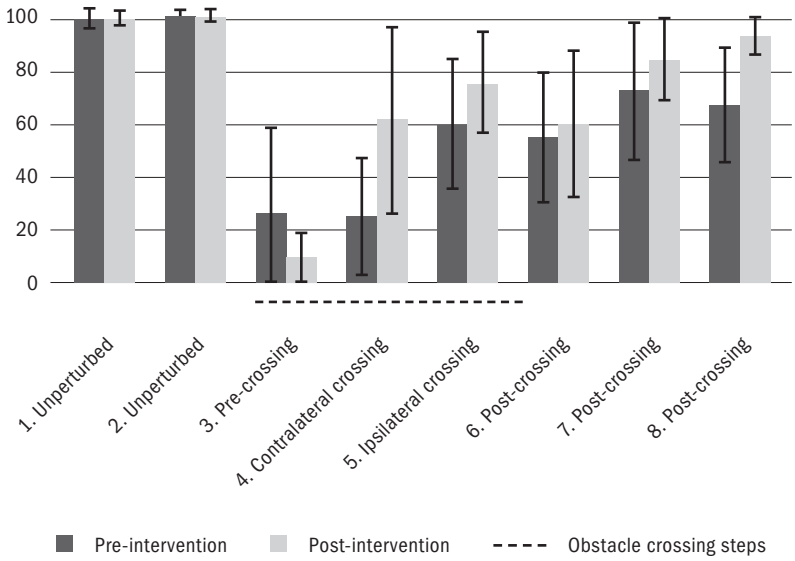

FIGURE 2.A Percentage of steps (±SD) in which the anterior-posterior margin of stability was within reference values. Values represent averages of all the participants (n = 10) for each step for the short step strategy. The dashed horizontal line indicates the obstacle crossing steps.

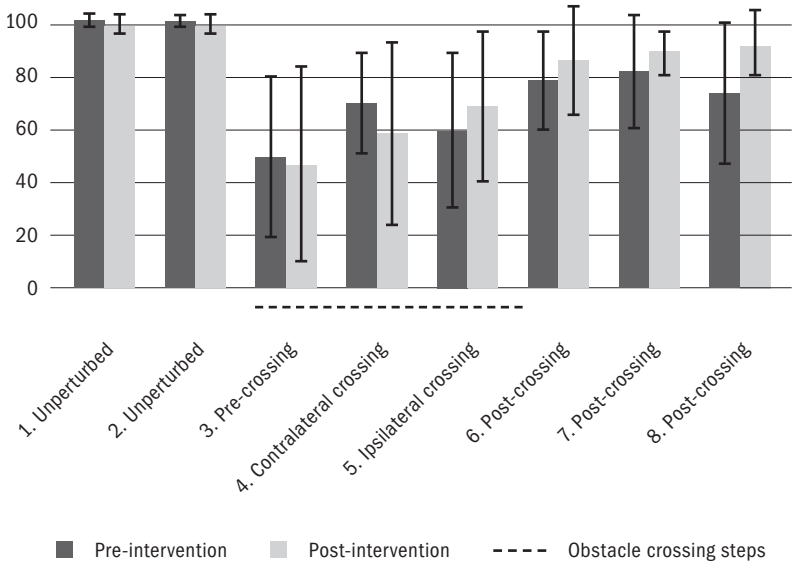

FIGURE 2.B Percentage of steps (±SD) in which the mediolateral margin of stability was within reference values.

Discussion

In this pilot study, we investigated the effect of gait adaptability training on obstacle avoidance and dynamic stability in patients with degenerative cerebellar ataxia. The training appeared to be feasible and was well appreciated by participants. After training, success rates on the obstacle avoidance task improved by 16 %. Patients more frequently used a short step strategy to cross obstacles. In order to shorten the step in front of the obstacle, participants reduced their dynamic stability in the sagittal plane. Post-intervention they tended to allow even greater reduction in dynamic stability in the shortened pre-crossing step. This presumably enabled them to avoid foot contact with the obstacle, as reflected in the higher success rates. However, their anterior-posterior MoS more effectively restored to their individual reference values in the subsequent steps. The maximum step width, peak-to-peak sway and mediolateral MoS did not change significantly, which implicates that the gain in dynamic stability in the sagittal plane did not come at the cost of increased lateral instability.

The increased use of the short step strategy to avoid the obstacle could not be explained by differences in task difficulty, since the available response time did not differ between pre- and post-intervention. This is in contrast with a study evaluating a similar training program in healthy elderly, in which a long step strategy was strongly preferred and this preference did not change over time.[26] It may be that, despite the relatively small sagittal-plane MoS during the pre-crossing step, the short step strategy is a safer strategy for obstacle avoidance

in patients with cerebellar ataxia as it requires a shorter time of single leg support compared to the long step strategy.

During overground walking beneficial effects of training were found on the obstacle subtask of the EFAP. Furthermore, we found improvements on the SARA total score after training. Although the SARA together with the International Cooperative Ataxia Rating Scale (ICARS) are the best studied ataxia scales, no study tried to define the Minimal Clinical Difference (MDC) or Minimal Clinically Important Differences (MCID) values of the SARA yet. Consequently, it is not clear to which extent a change of 0.4 points on the SARA is clinically meaningful. However, the mean annual change on the SARA is 1.38 points progression each year in patients with spinocerebellar ataxia, implying that without any training, no change or worsening of SARA scores was expected in the participants.[18]

These results demonstrate that gait adaptability training may lead to better whole-body coordination and not just improvement of lower limb ataxia alone. No improvement on the Berg Balance Scale was found, which might be due to the fact that this test contains many items in which the patients have to stand with a small base of support.

Studies in other neurological conditions imply that improvements in obstacle avoidance may also have clinically meaningful implications for daily life situations.[27] Furthermore, participants reported to experience more confidence in daily life situations and reported fewer falls, albeit not statistically significant due to the small sample size. The present findings suggest that C-Mill gait adaptability training has strong potential for improving safe community ambulation in patients with cerebellar ataxias.

This pilot study has some limitations. First, the study group was small and there was no control intervention. The latter is relevant, as one would like to test the hypothesis that, in ataxia patients, targeted training is more effective and tends to generalize more to daily practise than non-specific training. Furthermore participants may show improvement on the obstacle task without training, due to learning effects. However, possible learning effects were minimized by including a familiarization session in the week prior to the pretest. In addition, in a study evaluating the effects of an overground gait adaptability training program in community-dwelling elderly people, much smaller improvements were observed in the inactive control group (6%), compared to the 16% improvement in obstacle-avoidance success rates observed in the present study.[26]

Second, the question remains whether the results persist in the long-term and how they translate to activities of daily life and fall risk. Recent studies show a long-term effect of an intensive, high frequency training program, followed by chronic, less intensive and low-frequency training at home or at the physiotherapist's practice.[28, 29] Since long-term outcome appears to be influenced by training intensity at home, it may be that additional home exercises or continued challenging activities could enhance sustainment of the training-induced improvement.[29]

Generalization of the present findings to the group of patients with cerebellar ataxia at large may be limited, as our participants were able to walk independently and patients with mild ataxia seem to benefit more from training compared to patients with more severe ataxia.[28] Furthermore, this type and intensity of training program is less feasible for patients who are not able to walk or travel without assistance, which applies to half of the patients with spinocerebellar ataxia.[4]

In conclusion, this pilot study provides preliminary evidence of a beneficial effect of gait adaptability training on obstacle avoidance capacity and dynamic stability in patients with degenerative cerebellar ataxia. Therefore this study supports the recent findings that physiotherapeutic interventions in patients with cerebellar damage can be effective. Future studies should preferably include more patients and control interventions, with longer follow-up times to evaluate the sustainability of improvements, and also focus on the actual benefits of training on activities of daily life and fall frequency.

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Chapter 5

Summary and discussion

Cerebellar ataxia is characterized by disturbed coordination of movements, and manifests as gait and balance problems, falls, loss of dexterity, tremor and speech difficulties. There are many diseases that cause ataxia, but an important group is formed by the degenerative cerebellar ataxias. These disorders are progressive and untreatable, and often lead to a debilitating decrease in mobility, loss of independency and reduced quality of life. In daily practice, allied health care - and in particular physiotherapy - has an important role in the management of patients with degenerative ataxias.

The main goals of this thesis were: 1) to analyze the frequency, details and consequences of falls (which is one of the major targets for physiotherapy) in patients with dominantly inherited degenerative ataxias, 2) to evaluate the scientific evidence for allied health care interventions in cerebellar ataxia, 3) to examine the use and patient satisfaction of physiotherapy in patients with degenerative ataxias in the Netherlands, and to assess the level of expertise and needs of the physiotherapists who treat these patients, and 4) to explore the effect of gait adaptability training in patients with degenerative ataxia. This chapter summarizes and discusses the main findings of this thesis, together with some ideas and recommendations for future research and treatment.

Falls in cerebellar ataxias

Falls have been extensively studied in 'healthy' elderly and in patients with stroke, Parkinson's disease and neuromuscular diseases.[1-4] However, little was thus far known about falls in patients with degenerative ataxia.

Chapters 3.1 and **3.2** contain the results of the EuroSCA fall study, in which 228 patients with SCA1, SCA2, SCA3 or SCA6 completed a fall questionnaire about falls in the previous 12 months. 113 patients completed a falls dairy and filled in extra questionnaires about the first three falls between their annual visits to their neurologist. 73.6 percent of patients in the retrospective group and 81.4 percent of patients in the prospective group reported at least one fall in this period. Furthermore, the results showed that falls often had major consequences for these patients, including injuries and avoidance of activities due to a fear of falling. Factors that were associated with a higher fall frequency in the retrospective study included disease duration, severity of ataxia, the presence of pyramidal symptoms, the total number of non-ataxia symptoms, and the genotype SCA3. Factors associated with a lower fall frequency were the presence of extrapyramidal symptoms (more specifically dystonia of the lower limbs) and the genotype SCA2. The total number of non-ataxia symptoms and longer disease duration were independently associated with a higher fall frequency in a logistic regression analysis, while the presence of extrapyramidal symptoms was independently associated with a lower fall frequency. Falls also occurred in early stages of the disease. The prospective study confirmed that the presence of non-ataxia symptoms was associated with a higher fall frequency.

These results imply that neurologists and physiatrists should pay attention to falls and near-falls in the management of patients with degenerative ataxia. Fall prevention may include: stimulating the use of walking aids, raising awareness for the contributing factors, and reducing domestic hazards, for example by removing carpeting and providing hand grips. Training might be aimed at diminishing the fear of falling, learning how to attenuate the mechanical impact of the fall itself, to practice daily routines (including learning patients to make safe transfers), and to improve gait and balance. While most patients are referred to a physiotherapist for the fall training program, this has not been formally studied in great detail, and evidence-based training programs and guidelines are lacking. There is scientific evidence that exercise and individually tailored multifaceted intervention programs reduce falls in community dwelling older[5], and there are some indications that physiotherapy may reduce fall frequency in patients with multiple sclerosis.[6] In contrast, only fully supervised training seems to reduce fall frequency in patients with Parkinson's disease[7], and so far no effect of tailored multifaceted fall prevention programs in patients with stroke has been found.[8] Therefore, more research to assesses the effects of fall training and fall prevention in patients with cerebellar ataxia is warranted.

Our work showed that non-ataxia symptoms, especially the pyramidal symptoms, contribute to a higher fall frequency. Therefore, neurologists and physiatrists should take these symptoms into account when treating patients with cerebellar ataxia. However, it is currently unclear if the treatment of concomitant spasticity, with for example botulinum toxin injections, eventually leads to better balance and reduction of fall frequency. Furthermore, it would be interesting to see whether training aimed at contributing non-ataxia symptoms would result in a better clinical results.

When measuring any effect of future fall prevention programs, the question is what method to use for evaluating the frequency of falls. When comparing the prospective data with those of the retrospective study at the individual level, which was possible for 107 participants, differences in fall frequencies were found. More patients reported at least one fall in the fall diary (84.1 vs. 73.6 percent), but the overall fall frequency was lower. Also, in the prospective study, a lower frequency of near-falls was documented and a smaller proportion of the patients reported injuries in the fall diary. This might indicate that patients overestimate the frequency of falls and injuries retrospectively, or underreport (near-) falls and injuries in the fall diaries. Although these differences do not affect the main conclusions of the two fall studies, they do lead to questions with regard to the validity and applicability of the instruments used to measure falls. The use of an automated fall telephone system could be a more preferable method for this purpose[9], or the use of an online registration program or even an application on a smartphone or wearable device could be considered in the future[10, 11], as most patients will become accustomed to these devices.

Physiotherapy and training in ataxia

There is a general perception that patients with cerebellar ataxia are commonly referred for allied health care interventions, but data on how many patients were actually referred to and treated by a physiotherapist, and which methods were used were lacking. Furthermore, because guidelines for ataxia treatment are unavailable, it was imaginable that there is heterogeneity among the treatments provided. The lack of allied health care guidelines for ataxia is largely due to the unclear status of the scientific evidence that actually supports the instalment of such interventions. Work in the field of Parkinson's disease has demonstrated how important it is to assess current clinical practice in regards to allied health interventions,[12, 13] as this may serve for development of clinical practice guidelines,[14] inform the design of randomized clinical trials[15, 16] and help to optimize professional expertise.[17]

Chapter 4.1 describes the results of a systematic search for clinical trials concerning allied health care interventions in cerebellar ataxias.[14] trials were included, of which even the 4 best studies were formally only of moderate methodological quality. There was a wide variation in disorders included, sample sizes, types of intervention, and outcome measures. Most trials did not include a control intervention or control group. Overall, the studies indicate that physical therapy may lead to an improvement of ataxia symptoms and daily life functioning in patients with degenerative cerebellar ataxia, or with other diseases causing cerebellar ataxia. When added to physiotherapy, occupational therapy may improve global functional status, and occupational therapy alone might diminish symptoms of depression. There were insufficient data on speech and language therapy. So, although there is some evidence to apply physiotherapy and occupational therapy, properly designed and sufficiently large trials are needed and the results hereof will help to develop recommendations and guidelines for clinical practice.

Most studies included in the systematic review evaluated the effect of physiotherapy. In the majority of the studies, therapy was tailored to the individual, which is in accordance with therapeutic principles but this makes it difficult to generalize such interventions. Furthermore, often no control intervention was used, which complicates the interpretation of whether the observed improvement was related to the specific intervention, or to a more generalized and non-specific element of training. Physical therapy and occupational therapy are recommended for patients with cerebellar ataxia, based on two level 2 conclusions for physical therapy, and many level 3 conclusions for physical therapy and occupational therapy, based on the EBRO classification.[18] The relatively better studies suggest that physical training should be intensive, short, and adjusted to the needs and limitations of the patient, and that during and after such a program, patients

should be encouraged to practice at home. The extent to which the participants practised at home was related to the effect that was found, especially on the long term. These studies also suggested that treatment should start in earlier stages of disease, because those patients are more likely to benefit. Furthermore, since patients with degenerative cerebellar ataxia experience falls in early stages of the disease, physicians should be aware that training in patients with relatively mild symptoms may already be beneficial.

The studies available do allow the design of a potentially effective, feasible training program that should be tested in a randomized controlled study. If proven effective, such a program would serve as the basis for a practical guideline that can be implemented.

Another interesting finding was the positive effect of occupational therapy on depressive symptoms. It is known that patients with cerebellar pathology can have depressive symptoms.[19] as part of the so-called cerebellar cognitive affective syndrome (CCAS). CCAS is characterised by impairment of executive function, visuo-spatial processing, linguistic function and affective regulations, leading to problems with organizing activities, learning difficulties, communication problems and personality change.[20] Since psycho-active medication can worsen neurological symptoms due to side effects, including a markedly increase of the risk of falls[2, 21], it might be meaningful to examine to what extent allied health care therapies impact on CCAS features such as depressive symptoms. Furthermore, it could be interesting to assess whether the presence of depressive symptoms and cognitive deficits influence the effectiveness of such therapies, or whether possible functional improvements are driven primarily by a reduction of these non-motor symptoms.[22]

Chapter 4.2 describes the results of a study that evaluated utilisation, patient satisfaction and professional expertise of physiotherapy in degenerative cerebellar ataxias in the Netherlands. Questionnaires were sent to patients with degenerative cerebellar ataxias and, subsequently, questionnaires were sent to their physiotherapists. Eventually, 317 questionnaires from patients and 114 questionnaires from physiotherapists could be used for further assessment. 64 percent of the patients were currently treated by a physiotherapist. Their median treatment duration was 5 years. 19 percent of the patients had never been referred, often despite the presence of limitations in daily activities. On the other hand, some participants without reported limitations had received physiotherapy. Nearly one out of ten patients visited a physiotherapist without a referral by a physician. Patients' unwillingness to visit a physiotherapist increased with the severity of the problems experienced in the previous month, with reasons including 'not expecting benefits', 'doing own exercises' and 'lack of time'. The most commonly reported treatment goals were improvement or maintenance of balance, general physical condition, and mobility. The improvement experienced by patients ranged from 10.7 percent of patients

with (very) severe problems to 75 percent of the patient with no problems in functioning in the previous month. A third of the therapists reported improvement. In general, participants were satisfied with their physiotherapist, but patients who did not experience improvement of problems were less satisfied. Physiotherapists reported to have been treating a median of 2 patients with ataxia in the previous year, and they reported lack of ataxia-specific expertise and expressed the need for education and evidence-based guidelines.

This study shows that referral to and use of physiotherapy in patients with degenerative cerebellar ataxia in the Netherlands are inconsistent and suboptimal. Referral rates are high, but there is a discrepancy between referrals and actual indication for treatment. Patients with functional problems often do not use physiotherapy. More than half of the patients who had never been referred reported that physiotherapy had not been discussed by their physician. It is possible that physicians are not sufficiently aware of the possible benefit of physiotherapy or there may be a lack of time to screen for relevant indications in the clinic. Another interesting finding was that the proportion of patients who did not want to be referred was relatively larger in the group of patients who experienced more disabilities, up to 57 percent. This might be due to mobility problems, a fear to go outside, or cognitive problems, which could all hold patients back from travelling. Training at home, whether or not supervised by a physiotherapist, could be a solution for this specific group. Despite the specific functional impairments patients had reported on several domains, they had often not selected these items as a goal for treatment. Additionally, physiotherapists chose more training goals than their patients, but always included the goals selected by the patient. Consequently, better pre-treatment discussions between patient and therapist may lead to more specific training program and might increase patient satisfaction.

The consequences of the relatively low prevalence of patients with degenerative cerebellar ataxia are the relatively low caseload per physiotherapist, and the absence of specific training programs on top of the lack of evidence-based recommendations. So, as expected, physiotherapists reported a lack of ataxia-specific expertise, and they used measurement instruments that have not been designed for patients with ataxia to evaluate the training effect. Therefore, concentration of care is essential to optimize treatment of patients with ataxia. The ataxia field could adopt the approach of ParkinsonNet, a Dutch professional network of allied health care workers who have received specific training in Parkinson's disease, and who attract a high caseload of these patients.[17]

Treatment duration was long and training methods were not in accordance with the limited scientific evidence that was actually available. The majority of physiotherapists believed that chronic treatment on a weekly basis is needed for their patients. This is in contrast to what the literature is suggesting, namely that it might be more effective to start an intensive, high frequency training program first,

followed by less intensive and low-frequency training at home or at the physiotherapist's practice. In order to make such training programs feasible, it could be useful to refer a patient to a specialized physiotherapist or rehabilitation center first, followed by a tailored treatment plan taken over by general physiotherapists. Again, more research is warranted to develop the best training protocols and eventually evidence-based guidelines and the implementation thereof.

We then went on to test a very specific component of a putative training program for patients with ataxia. Adjustment of gait patterns to variable requirements of the environment is essential to avoid falls, and we wanted to examine whether gait adaptability training might be useful for patients with cerebellar ataxia.

In **chapter 4.3**, the results of a pilot study that evaluated the effect of gait adaptability training on obstacle avoidance and dynamic stability in patients with degenerative cerebellar ataxia are described. Ten patients received 10 protocolised gait adaptability training sessions of 1 hour each for 5 weeks. Training was performed on a treadmill with visual stepping targets and obstacles projected on the belt's surface. As the primary outcome measure, an obstacle avoidance task while walking on a treadmill was used. An embedded force platform, video recordings, and 3D-markers were used to assess avoidance success rates and dynamic stability during the obstacle avoidance tasks. Patients also performed clinical tests including the Scale for the Assessment of Ataxia (SARA), the 10 meter walking test, the Timed Up-and-Go Test, the Berg Balance Scale, and the obstacle subtask of the Emory Functional Ambulation Profile (EFAP). After the training, success rates on the obstacle avoidance task had improved by 16 percent compared to pre-intervention. For successful avoidance, participants allowed themselves smaller stability margins in the sagittal plane, while using a shortened pre-crossing step more often. However, in the subsequent steps they returned to baseline stability values more quickly than before training. SARA scores and the EFAP obstacle subtask also improved significantly. Participants reported to experience more confidence in daily life situations and reported fewer falls, albeit not statistically significant, probably due to the small sample size in this pilot study.

This pilot study showed a beneficial effect of gait adaptability training on obstacle avoidance capacity and dynamic stability in patients with cerebellar degeneration, which suggests a potential for improving safe daily life ambulation. In a study evaluating a similar training program in healthy elderly, not only a positive effect on obstacle avoidance capacity was found, but also on the frequency of falls.[23] A long-step strategy was strongly preferred by the healthy elderly and this preference did not change over time, while patients with cerebellar ataxia in this study more frequently used a short-step strategy after training. These

results cautiously suggest that this type of gait adaptability training could be part of training programs for ataxia patients. Yet, future studies should include more patients and control interventions, have longer follow-up times to evaluate the sustainability of improvements, and assess whether the results translate to actual benefit in daily life (such as a reduction of falls). The gait adaptability training used in this pilot study was well appreciated by participants, in particular the gaming element at the end of each training session, which combined the different exercises patients had practised. The problem is that this type of training, in this specific set-up, is not possible at home. A more feasible option could be whole-body training based on recently developed and commercially available videogame technology, under supervision by a physiotherapist.[24, 25] Additionally, by using these videogames, a more feasible training program for patients who are not able to walk or travel without assistance could be designed.

An interesting neurobiological issue is the question why such types of training lead to improvement. We suspect that training, alongside other effects, triggers cerebral changes and more specifically boosts cerebral compensatory mechanisms. To investigate this, we are now doing a follow-up study in which patients undergo functional MRI scanning before and after this training protocol. We hope to extract the cerebral compensatory mechanisms in patients with a cerebellar defect. A next step could then be to try and stimulate these compensatory areas with neuromodulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), and to test whether such interventions, as an add-on to training, have synergistic effects.[26, 27]

In conclusion, cerebellar ataxia has major consequences for daily life, of which falls are a clear example. It makes sense to refer patients for physiotherapy or other forms of training, but the actual scientific evidence to support this is limited. Patients are being referred, but there is mismatch between necessity and usage, treatment programs are very heterogeneous, and therapists lack specific expertise. Good quality trials are needed, also as an important first step to develop evidence-based guidelines for allied healthcare interventions. When such guidelines become available, therapists can be trained, and in this regard, we can learn from the model used by ParkinsonNet, aiming at delivering the best possible multidisciplinary treatment.[17, 28, 29] This way of organizing care will make it easier for both patients and physicians to select the most appropriate therapist to refer to, and might improve quality of care, possibly even at lower societal costs.

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Chapter 6

Dutch Summary – Nederlandse samenvatting

Cerebellaire ataxie is een neurologische bewegingsstoornis, die met name gekenmerkt wordt door coördinatieproblemen. Deze uiten zich als balans- en loopproblemen, vallen, slik- en spraakstoornissen en verminderde handvaardigheid. Ataxie kan door verscheidene ziekten worden veroorzaakt.

Hoofdstuk 1 geeft een overzicht van deze ziekten met een praktische leidraad hoe men in de dagelijkse praktijk tot een diagnose en behandelplan kan komen. Belangrijk hierbij zijn een gedegen anamnese en een aantal specifieke bevindingen bij het lichamelijk onderzoek. Indien een MRI-scan van de hersenen structurele pathologie heeft uitgesloten, zijn inflammatoire en heredodegeneratieve stoornissen de twee meest voorkomende etiologische groepen.

De in dit proefschrift beschreven studies richtten zich op de heredodegeneratieve ataxieën. Deze aandoeningen zijn progressief en leiden tot een verminderde mobiliteit, vallen en een afname van de kwaliteit van leven. Ten gevolge van het ontbreken van medicamenteuze behandelopties speelt de paramedische hulpverlening een belangrijke rol in de behandeling van deze ziekten. Er was echter weinig bekend over in welke mate en op welke wijze fysiotherapie werd toegepast bij deze groep van patiënten. Tevens was er weinig wetenschappelijk bewijs voor deze behandeling voorhanden, met als gevolg hiervan ook een gebrek aan richtlijnen voor deze patiëntengroep.

Hoofdstuk 2 De belangrijkste doelen van dit proefschrift waren:

- het in kaart brengen van de incidentie, details en gevolgen van vallen in patiënten met autosomaal-dominante cerebellaire ataxieën,
- het verzamelen en beoordelen van wetenschappelijke studies betreffende paramedische interventies voor cerebellaire ataxie,
- het verkrijgen van meer inzicht in het gebruik van fysiotherapie, de tevredenheid van patiënten, de mate van expertise en de behoeften van fysiotherapeuten die deze patiënten behandelen.

Tevens werden de effecten van een specifieke looptraining bij patiënten met een degeneratieve ataxie onderzocht.

Hoofdstuk 3.1 en **hoofdstuk 3.2** beschrijven de resultaten van de EuroSCA-valstudie. 228 Patiënten met SCA1, SCA2, SCA3 of SCA6 vulden een vragenlijst in over vallen in de voorafgaande twaalf maanden. 113 patiënten hielden een valdagboek bij tussen hun jaarlijkse bezoeken aan hun behandelend neuroloog en vulden hiernaast ook vragenlijsten in over de eerste drie vallen. 73,6 procent van de patiënten in de retrospectieve groep en 81,4 procent van de patiënten in de prospectieve groep rapporteerden ten minste één val in deze periode. De resultaten toonden aan dat vallen verschillende gevolgen had voor de patiënten, waaronder letsels en het vermijden van activiteiten ten gevolge van angst om te vallen. Factoren die geassocieerd waren met een hogere valfrequentie in de retrospectieve studie waren ziekteduur, ernst van de ataxie, de aanwezigheid van pyramidale verschijnselen, het totale aantal symptomen anders dan ataxie en

het genotype SCA3. Factoren geassocieerd met een lagere valfrequentie waren de aanwezigheid van extrapiramidale verschijnselen (en dan vooral dystonie van de onderste ledematen) en het genotype SCA2. Het totaal aantal niet-ataxie symptomen en langere ziekteduur waren onafhankelijk geassocieerd met een hogere valfrequentie in een logistische regressieanalyse, terwijl de aanwezigheid van extrapiramidale verschijnselen onafhankelijk geassocieerd was met een lagere valfrequentie. Ook bleek dat valllen ook in de vroege stadia van de ziekte voorkomt. De prospectieve studie bevestigde dat de aanwezigheid van niet-ataxie symptomen geassocieerd is met een hogere valfrequentie.

Deze resultaten dragen bij aan de 'awareness' bij hulpverleners (en patiënten) over het hoge valrisico bij deze patiënten en helpen ook om die ataxiepatiënten met een grotere kans op vallen te identificeren.

Hoofdstuk 4.1 bevat een literatuurstudie naar klinisch onderzoek met betrekking tot paramedische interventies bij cerebellaire ataxie. 14 studies werden geselecteerd, waarvan de vier beste studies formeel als van matige methodologische kwaliteit beoordeeld werden. Er was een grote variatie in ziektebeelden, aantal onderzochte patiënten, soorten interventies en uitkomstmaten. De meeste studies hadden geen controle-interventie gebruikt.

De studies suggereren dat fysiotherapie kan leiden tot een vermindering van de ataxie en een verbetering kan geven van ADL- functies bij patiënten met een degeneratieve cerebellaire ataxie, en andere ziekten die gepaard gaan met cerebellaire ataxie. Wanneer uitgevoerd in combinatie met fysiotherapie, kan ergotherapie het algemene functioneren verbeteren en ergotherapie alleen zou symptomen van een depressie kunnen verminderen. Er waren onvoldoende studies over logopedie. Er werd dus enig bewijs voor de toepassing van fysiotherapie en ergotherapie bij ataxie gevonden, maar meer studies van betere kwaliteit zijn nodig om aanbevelingen te doen en richtlijnen voor de klinische praktijk te ontwikkelen.

Hoofdstuk 4.2 beschrijft de resultaten van een onderzoek naar fysiotherapie bij degeneratieve cerebellaire ataxieën in Nederland. Hierbij werd gekeken naar de mate van gebruik van fysiotherapie, de tevredenheid van patiënten hierover en de professionele expertise van de fysiotherapeuten. Er werden vragenlijsten aan patiënten met een autosomaal-dominante cerebellaire ataxie gestuurd en vervolgens werd ook een vragenlijst aan hun fysiotherapeuten verzonden. Uiteindelijk konden 317 vragenlijsten van patiënten en 114 vragenlijsten van fysiotherapeuten gebruikt worden voor verdere analyse. 64 procent van de patiënten werden op dat moment behandeld door een fysiotherapeut. Hun gemiddelde behandelingsduur was 5 jaar. 19 procent van de patiënten was nog nooit verwezen, vaak ondanks de aanwezigheid van beperkingen in hun dagelijkse activiteiten. Anderzijds werden sommige deelnemers zonder beperkingen al wel door een fysiotherapeut behandeld. Bijna één op de tien patiënten bezocht een fysiotherapeut zonder verwijzing van een arts. Het aantal

patiënten die geen fysiotherapeut wensten te bezoeken nam toe met de ernst van de problemen in de voorgaande maand. De genoemde redenen waren onder andere ‘geen verwachte voordelen',' zelf oefeningen doen' en 'gebrek aan tijd'. De meest gerapporteerde behandelingsdoelen waren verbetering of onderhoud van de balans, de algemene fysieke conditie en mobiliteit. Het aantal patiënten dat verbetering bemerkte varieerde van 10,7 procent van de patiënten met (zeer) ernstige problemen tot 75 procent van de patiënten zonder problemen in functioneren in de voorgaande maand. Eén derde van de therapeuten rapporteerde verbeteringen bij hun patiënten. In het algemeen waren de deelnemers tevreden over hun fysiotherapeut. Patiënten die geen verbetering van de problemen ondervonden waren minder tevreden. Fysiotherapeuten behandelden gemiddeld 2 patiënten met ataxie in het voorgaande jaar. Ze vermeldden een tekort aan ataxie-specifieke expertise en gaven aan behoefte te hebben aan onderwijs en evidence-based richtlijnen.

Dit onderzoek toont dus dat de behandeling van fysiotherapie bij ataxie gerichter moet worden ingezet en dat er op studies gebaseerde richtlijnen moeten komen met daaraan gekoppelde scholing voor therapeuten.

In **hoofdstuk 4.3** worden de resultaten van een pilotstudie beschreven, die het effect van een looptraining bij patiënten met degeneratieve cerebellaire ataxie beschreven. De looptraining richtte zich op het loopspecifieke aanpassingsvermogen om obstakels te ontwijken en op de dynamische stabiliteit. Tien patiënten kregen 10 geprotocolleerde trainingen van telkens 1 uur gedurende 5 weken. De training werd uitgevoerd op een loopband waarbij visuele stappen, doelen en obstakels geprojecteerd werden op het oppervlak van de loopband. Als primaire uitkomstmaat werd een ‘obstakel vermijdings-taak’ tijdens het lopen op een loopband gebruikt. Een ingebouwd krachtplatform, video-opnames en 3D-markers werden gebruikt voor de beoordeling van de succespercentages van het vermijden van het obstakel en de dynamische stabiliteit tijdens deze taak. Er werden ook klinische scores afgenomen zoals de Scale for the Assessment of Ataxia (SARA-score), de 10 meter looptest, de Timed Up-and-Go Test, de Berg Balance Schaal en het obstakelonderdeel van de Emory Functional Ambulation Profile (EFAP). Na de training waren de succespercentages op het vermijden van de obstakels met 16 procent toegenomen ten opzichte van voor de training. Om succesvol de obstakels te kunnen vermijden, lieten deelnemers een verminderde stabiliteit toe in het voorachterwaartse vlak, terwijl een verkorte stap voor het obstakel vaker werd toegepast. In de daaropvolgende stappen keerden de stabiliteitswaarden sneller terug naar de beginwaarden dan voor de training. De SARA-scores en de prestatie op het EFAP obstakelonderdeel verbeterden aanzienlijk. Hoewel niet statistisch significant (waarschijnlijk vanwege de kleine groep), gaven deelnemers aan meer vertrouwen tijdens situaties in het dagelijkse leven te ervaren en rapporteerden ze minder te vallen.

Concluderend is 1) vallen een veelvoorkomend probleem bij patiënten met ataxie, met soms ook ernstige gevolgen, 2) een specifieke looptraining nuttig bij patiënten met ataxie, mogelijk ook voor het vallen, maar is meer onderzoek nodig o.a. naar het beste trainingsprotocol en 3) er een behoefte aan een behandelrichtlijn en scholing voor fysiotherapeuten specifiek voor ataxie.

Appendices

Dankwoord

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Curriculum vitae

Ella Fonteyn werd op 14 mei 1983 in Weert geboren. In 2001 behaalde zij haar VWO-diploma aan het Bisschoppelijk College in Weert. In hetzelfde jaar begon ze aan de studie geneeskunde aan de Radboud Universiteit in Nijmegen. Haar belangstelling voor ataxie werd gewekt tijdens een introductie co-schap op de afdeling kinderneurologie in het Radboudumc, onder begeleiding van onder andere Bart van de Warrenburg. In 2007 sloot ze dan ook haar studie geneeskunde af met een wetenschappelijk stage op de afdeling neurologie van het Radboudumc, met een onderzoek naar vallen bij degeneratieve cerebellaire ataxieën onder supervisie van Bart van de Warrenburg. Aansluitend ging zij aan de slag als arts-assistent niet in opleiding neurologie in het Jeroen Bosch Ziekenhuis in Den Bosch en een jaar later als poortarts in hetzelfde ziekenhuis. Eind 2009 begon zij aan de opleiding tot neuroloog in het Canisius-Wilhelmina Ziekenhuis in Nijmegen (opleider Wim Verhagen). Tijdens deze opleiding bleef ze met enthousiasme wetenschappelijk onderzoek verrichten, hetgeen resulteerde in dit proefschrift. Naast bewegingsstoornissen heeft ze belangstelling voor de klinische neurofysiologie en hoofdpijn. In 2016 rondde zij haar opleiding tot neuroloog af en vanaf april 2016 is ze werkzaam als neuroloog en klinisch neurofysioloog in het Universitair Medisch Centrum Utrecht.

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88. Joosten-Weyn Banningh, L.W.A. (2012). Learning to live with Mild Cognitive Impairment: development and evaluation of a psychological intervention for patients with Mild Cognitive Impairment and their significant others. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
89. Xiang, HD. (2012). The language networks of the brain. Radboud University Nijmegen, Nijmegen, the Netherlands.
90. Snijders, A.H. (2012). Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
91. Rouwette, T.P.H. (2012). Neuropathic pain and the brain - Differential involvement of corticotropin-releasing factor and urocortin 1 in acute and chronic pain processing. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
92. Van de Meerendonk, N. (2012). States of indecision in the brain: Electrophysiological and hemodynamic reflections of monitoring in visual language perception. Radboud University Nijmegen, Nijmegen, the Netherlands.
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100. Meeuwissen, E.B. (2012). Cortical oscillatory activity during memory formation. Radboud University Nijmegen, Nijmegen, The Netherlands.
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116. Van Dongen, E.V. (2013). Sleeping to Remember. On the neural and behavioral mechanisms of sleep-dependent memory consolidation. Radboud University Nijmegen, Nijmegen, The Netherlands.
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123. Eskenazi, T.T. (2013). You, us & them: From motor simulation to ascribed shared intentionality in social perception. Radboud University Nijmegen, Nijmegen, The Netherlands.
124. Ondobaka, S. (2013). On the conceptual and perceptual processing of own and others' behavior. Radboud University Nijmegen, Nijmegen, The Netherlands.
125. Overvelde, J.A.A.M. (2013). Which practice makes perfect? Experimental studies on the acquisition of movement sequences to identify the best learning condition in good and poor writers. Radboud University Nijmegen, Nijmegen, The Netherlands.
126. Kalisvaart, J.P. (2013). Visual ambiguity in perception and action. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
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130. Braakman, M. H. (2013). Posttraumatic stress disorder with secondary psychotic features. A diagnostic validity study among refugees in the Netherlands. Radboud University Nijmegen, Nijmegen, The Netherlands.
131. Zedlitz, A.M.E.E. (2013). Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment. Radboud University Nijmegen, Nijmegen, The Netherlands.
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133. Jansen, D. (2013). The role of nutrition in Alzheimer's disease - A study in transgenic mouse models for Alzheimer's disease and vascular disorders. Radboud University Nijmegen, Nijmegen, The Netherlands.
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135. Severens, M. (2013). Towards clinical BCI applications: Assistive technology and gait rehabilitation. Radboud University Nijmegen, Nijmegen, Sint Maartenskliniek, Nijmegen, The Netherlands.
136. Bergmann, H. (2014). Two is not always better than one: On the functional and neural (in)dependence of working memory and long-term memory. Radboud University Nijmegen, Nijmegen, The Netherlands.
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139. Brazil, I.A. (2013). Change doesn't come easy: Dynamics of adaptive behavior in psychopathy. Radboud University Nijmegen, Nijmegen, The Netherlands.
140. Zerbi, V. (2013). Impact of nutrition on brain structure and function. A magnetic resonance imaging approach in Alzheimer mouse models. Radboud University Nijmegen, Nijmegen, The Netherlands.
141. Delnooz, C.C.S. (2014). Unravelling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
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147. Radke, S. (2014). Acting social: Neuroendocrine and clinical modulations of approach and decision behavior. Radboud University Nijmegen, Nijmegen, The Netherlands.
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149. Kok, P. (2014). On the role of expectation in visual perception: A top-down view of early visual cortex. Radboud University Nijmegen, Nijmegen, The Netherlands.
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152. Wester, A. (2014). Assessment of everyday memory in patients with alcohol-related cognitive disorders using the Rivermead Behavioural Memory Test. Radboud University Nijmegen, Nijmegen, The Netherlands.
153. Koenraadt, K. (2014). Shedding light on cortical control of movement. Radboud University Nijmegen, Nijmegen; Sint Maartenskliniek, Nijmegen, The Netherlands.
154. Rutten-Jacobs, L.C.A. (2014). Long-term prognosis after stroke in young adults. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
155. Herbert, M.K. (2014). Facing uncertain diagnosis: the use of CSF biomarkers for the differential diagnosis of neurodegenerative diseases. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
156. Llera Arenas, A. (2014). Adapting brain computer interfaces for non-stationary changes. Radboud University Nijmegen, Nijmegen, The Netherlands.
157. Smulders, K. (2014). Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
158. Boyacioglu, R. (2014). On the application of ultra-fast fMRI and high resolution multiband fMRI at high static field strengths. Radboud University Nijmegen, Nijmegen, The Netherlands.
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163. Aerts, M.B. (2014). Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
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175. Meyer, M.C. (2015). “In between Modalitiers combined EEG – fMRI”. Radboud University, Nijmegen, The Netherlands.
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182. Meijer, F.J.A. (2015). Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging. Radboud university medical center, Nijmegen, The Netherlands.
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200. Blokland, Y. M. (2015). Moving towards awareness detection: From Brain-Computer Interfacing to anaesthesia monitoring. Radboud University, Nijmegen, The Netherlands.
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209. Ly, V. (2016). Affective biasing of instrumental action: How emotion shapes behaviour. Radboud University, Nijmegen, The Netherlands/ Radboud University Medical Center, Nijmegen, The Netherlands.
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211. Bouman Z. (2016). A measure to remember: Adaptation, standardization and validation of the Dutch version of the Wechsler Memory Scale - Fourth Edition (WMS-IV-NL). Radboud University, Nijmegen, The Netherlands/ Radboud University Medical Center, Nijmegen, The Netherlands.
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216. Bruggink, K. (2016). Amyloid-beta and amyloid associated proteins in the pathogenesis and diagnosis of Alzheimer's Disease. Radboud University Medical Center, Nijmegen, The Netherlands or Radboud University Medical Center, Nijmegen, The Netherlands.
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224. Aalbers, T. (2016). eHealth in the primary prevention of cognitive decline; The Brain Aging Monitor study. Radboud University Medical Center, Nijmegen, The Netherlands
225. Fonteyn, E. (2016). Falls, physiotherapy and training in patients with cerebellar degeneration. Radboud University Medical Center, Nijmegen, The Netherlands.

Dissertations of the disorders of movement research group, Nijmegen

Parkinson Center Nijmegen (ParC)

- Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, 17 June 2008
- Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, 27 May 2009
- W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, 7 October 2009
- Samyra H.J. Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, 29 April 2010
- Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, 29 November 2010
- Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, 29 November 2010
- Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, 24 May 2011
- Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, 6 December 2011
- Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, 22 December 2011
- Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen,4 June 2012
- Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, 22 November 2012
- Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 13 February 2013
- Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 6 March 2013
- Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, 6 March 2013
- Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, 6 June 2013
- Marjolein A van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, 10 January 2014
- Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, 21 May 2014
- Marjolein B. Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, 27 June 2014
- Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, 13 February 2015
- Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, 23 June 2015
- Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, 2 September 2015
- Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, 1 December 2015
- Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, 11 February 2016
- Merel M. van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, 13 April 2016

Non-Parkinsonian disorders of movement

- Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, 5 April 2012
- Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, 20 December 2013
- Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, 7 January 2014

Vascular disorders of movement – The Radboud Stroke centre

- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
- Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011
- Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012
- Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, 14 April 2014
- Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, 12 June 2015

Neuromuscular disorders of movement

- Mireille van Beekvelt. Quantitative near infrared spectroscopy (NIRS) in human skeletal muscle. Radboud University Nijmegen, 24 April 2002
- Johan Hiel. Ataxia telangiectasia and Nijmegen Breakage syndrome, neurological, immunological and genetic aspects. Radboud University Nijmegen, 23 April 2004
- Gerald JD Hengstman. Myositis specific autoantibodies, specificity and clinical applications. Radboud University Nijmegen, 21 September 2005
- M. Schillings. Fatigue in neuromuscular disorders and chronic fatigue syndrome, a neurophysiological approach. Radboud University Nijmegen, 23 November 2005
- Bert de Swart. Speech therapy in patients with neuromuscular disorders and Parkinson's disease. Diagnosis and treatment of dysarthria and dysphagia. Radboud University Nijmegen, 24 march 2006
- J. Kalkman. From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model. Radboud University Nijmegen, 31 October 2006
- Nens van Alfen. Neuralgicamyotrophy. Radboud University Nijmegen, 1 November 2006
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