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Netherton syndrome; neuropsychological and psychosocial functioning of child and adult patients and their parents

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Abstract

Background: Netherton syndrome is a rare severe skin disease. Clinical experience showed considerable psychosocial burdens among Netherton syndrome patients/families. Their (neuro)psychological functioning has never been investigated.

Objective: To investigate neuropsychological/psychosocial functioning of Netherton syndrome patients and parents.

Methods: A total of 12 Netherton syndrome patients and/or parents completed neuropsychological tests, semi-structured-interviews, and psychological-questionnaires.

Results: Intelligence results showed disharmonic profiles, with below-average scores on processing speed. Neuropsychological problems and unfavorable outcomes on health-related quality of life, illness-appearance-related problems, and negative social consequences among patients/parents were found. Psychopathological (emotional) problems were reported; stigmatization, bullying was common among Netherton syndrome patients.

Conclusion: Compared with normative data, Netherton syndrome patients showed neuropsychological and psychosocial problems. Standard follow-up is necessary to identify problems at early stage.

Keywords

adults, children, Netherton syndrome, neuropsychological, parents, psychosocial, skin

Introduction

Netherton syndrome (NS) is a severe rare and autosomal recessive disease, caused by mutations in the serine peptidase inhibitor Kazal-type 5 (SPINK5) gene. SPINK5 encodes the lympho-epithelial Kazal-type-related inhibitor (LEKT1) protein, which, if absent, results in a damaged

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skin barrier (Hovnanian, 2013). NS is classified as an ichthyosis and occurs in 1:200.000 newborns, first described in 1947 by Comél (Blume-Peytavi, 2008; Carrick et al., 2007). Most times, affected individuals present at birth with erythroderma (red and scaly skin). Due to the impaired skin barrier, patients are at risk for recurring infections and dehydration. In infancy, this results in a high risk of mortality and morbidity. The erythroderma persists in some patients, in other patients evolves into ichthyosis linearis circumflexa or into a combination of these and might be complicated by skin infections (Chavanas et al., 2004). These patients have skin symptoms, generalized pruritus (itch) and pain as part of a chronic relapsing course. Topical treatment of the skin usually includes emollient and mild immunosuppressive agents and if indicated combined with (topical) antibiotics (AB). Besides this, patients have impaired growth, specific hair shaft defect, trichorrhexis invaginata, atopic constitution, and an immune deficiency (Furio and Hovnanian, 2014; Renner et al., 2009). The treatment is mainly symptomatic.

In the literature, hardly anything has been described about neuropsychological or psychosocial functioning of patients with NS. So far, only a few studies, performed in the 70s–80s by Julias and Keeran (1971) and Caputo (1984), described cognitive problems (mental retardation) in three male patients with NS. No systematic studies have been performed to investigate neuropsychological or psychosocial functioning. From clinical experience, the psychosocial burden of NS often results in difficulties for patients and their families. NS causes itch, pain/wounds, risk of infections, fear of death in the first year of life, fear of side effects, fatigue, sleeping problems, self-esteem problems, and stigmatization due to the visibility of the condition. In addition, the severity of affected skin changes over time in NS, making it difficult for patients to adapt each time to the new situation. Besides, the impact of the therapy for the skin (emollient therapy and bathing at least twice a day) is large. For young children, the physical care for the skin should be done by parents, which forms a tiresome challenge. In adolescence/adulthood, this time-consuming therapy is performed by patients themselves. In addition, disease-related physical care and worries regarding the patients' future remain a difficult task for parents, certainly when there are more children in the family. For patients with NS and their parents, the severe skin symptoms seem to form a huge psychological and psychosocial burden.

Most studies concerning the psychological and psychosocial impact on patients with a visible skin disease focused on psoriasis and atopic dermatitis. Compared with the general population, patients with these skin diseases indicated reduced well-being, quality of life, and psychological problems like anxiety and depression (Dures et al., 2001; Lewis-Jones and Finlay, 1995; Verhoeven et al., 2007). The psychosocial impact due to visibility like bullying, social exclusion, fearful anticipation in social activities, emotional burden, and shame due to a deviant appearance also has been described by Lovegrove and Rumsey (2005), Magin et al. (2008), Rumsey and Harcourt (2004), and Tuckman (2017). A study in families of patients with atopic dermatitis showed that the quality of life was affected by the increasing disruption of family functions, affecting family dynamics and family life in general (Shobaili, 2010). Parents of children with skin diseases evaluated the quality of life of their child as lower than parents of children with a chronic disease like asthma or diabetes (Beattie and Lewis-Jones, 2006).

The present study aims to investigate the neuropsychological and psychosocial functioning of patients with NS and their parents. Based on clinical experience and the few research studies available, we hypothesized to find psychosocial problems for patients with NS and their parents, possibly due to deviant appearance, psychological, social, and physical discomfort. Furthermore, we hypothesized to find neuropsychological problems, possibly due to multiple infections or insufficient benefit of education, due to discomfort of the disease.

Methods

Patients' cohort and definitions

Recruitment strategy. This study was performed at the Erasmus Medical Center Rotterdam-Sophia Children's Hospital, an academic center of expertise for rare skin diseases (specifically NS), approved by the Dutch Ministry of Health (VWS). The study was conducted by the multidisciplinary Netherton team including psychologists of the department of Child and Adolescent Psychiatry/Psychology, Unit Psychosocial Care. All patients known with NS in the Dutch population and their parents were considered eligible. No exclusion criteria were applied.

Ethics. The study was approved by the local medical ethical review committee. Written informed consent was obtained from parents and children (if >12 years old) and by adult patients themselves (>18 years and older).

Procedure. Between June and December 2016, participating patients were invited for an extensive neuropsychological assessment and a semi-structured interview in the outpatient clinic, 3–23 years after having been diagnosed with NS. At the same time, the parents of the participating patients were invited for an interview, in the outpatient clinic or by telephone. Patients and parents were also asked to complete questionnaires at home, on health-related quality of life (HR-QoL), social, emotional, and behavioral functioning. Choice of the parental informant (mother/father) was left to the parents and patients themselves.

Assessment tools

Dutch versions of internationally validated intelligence and neuropsychological tests and questionnaires (child/adult versions) were used, covering the corresponding age ranges of participants. Scores on the intelligence (Mean (M) = 100, standard deviation (SD) = 15) and neuropsychological (M = 50, SD = 10) tests were compared with normative data from representative Dutch general population samples with corresponding gender and age categories. Higher scores meant favorable outcomes (for translation of scales Figure 1). Evaluation of intellectual functioning was reported with age-appropriate versions of the Wechsler Intelligence Scale (Wechsler Intelligence Scale for Children-III (WISC-III), Wechsler Adult Intelligence Scale-IV (WAIS-IV)), measured intelligence and cognitive ability (Kort et al., 2005; Wechsler, 2012). Short- and long-term verbal memory was evaluated with the 15 Words Test (15 WT), measuring verbal memory and learning ability (Bouma et al., 2012; Van den Burg and Kingma, 1999). Short- and long-term visuo-spatial memory was evaluated with the Rey–Osterrieth Complex Figure Test (ROCF), measuring visuo-spatial abilities, visual memory, visual attention, planning, and working memory (Meyers and Meyers, 1995; Rey, 1964). Executive function (EF) was evaluated with the Stroop Color Word Test (SCWT) (Brink, 1984; Schmand et al., 2005), measuring alternated attention, interference phenomena, and mental speed, and with the Trail Making Test (TMT), measuring visual attention and task switching (Lezak, 1995; Schmand et al., 2005). Attention was evaluated with the attention and concentration test (D2), measuring selective and sustained attention and visual scanning speed (Brickencamp and Oosterveld, 2011).

The semi-structured Rotterdam Quality of Life interview (Utens and Versteegh, 2014) was completed by patients and parents. This interview has been applied in studies regarding medically ill children, adolescents, and adults (Dulfer, 2014; Opic et al., 2016). It included questions on biographical characteristics. NS-related questions have been added regarding current physical problems (fatigue, pain, itching, etc.), psychosocial functioning (living, work, school/study, leisure time, etc.), appearance-related difficulties, attachment, and limitations (for translation of items, see Tables 1 to 3).

Scores on questionnaires were compared with normative data from representative Dutch general population samples (for translation of scales, see Figure 2 to 4, Tables 4 and 5. Emotional and behavioral problems in children were assessed with Dutch version of the Child Behavior Checklist—parent version (CBCL) and for adults

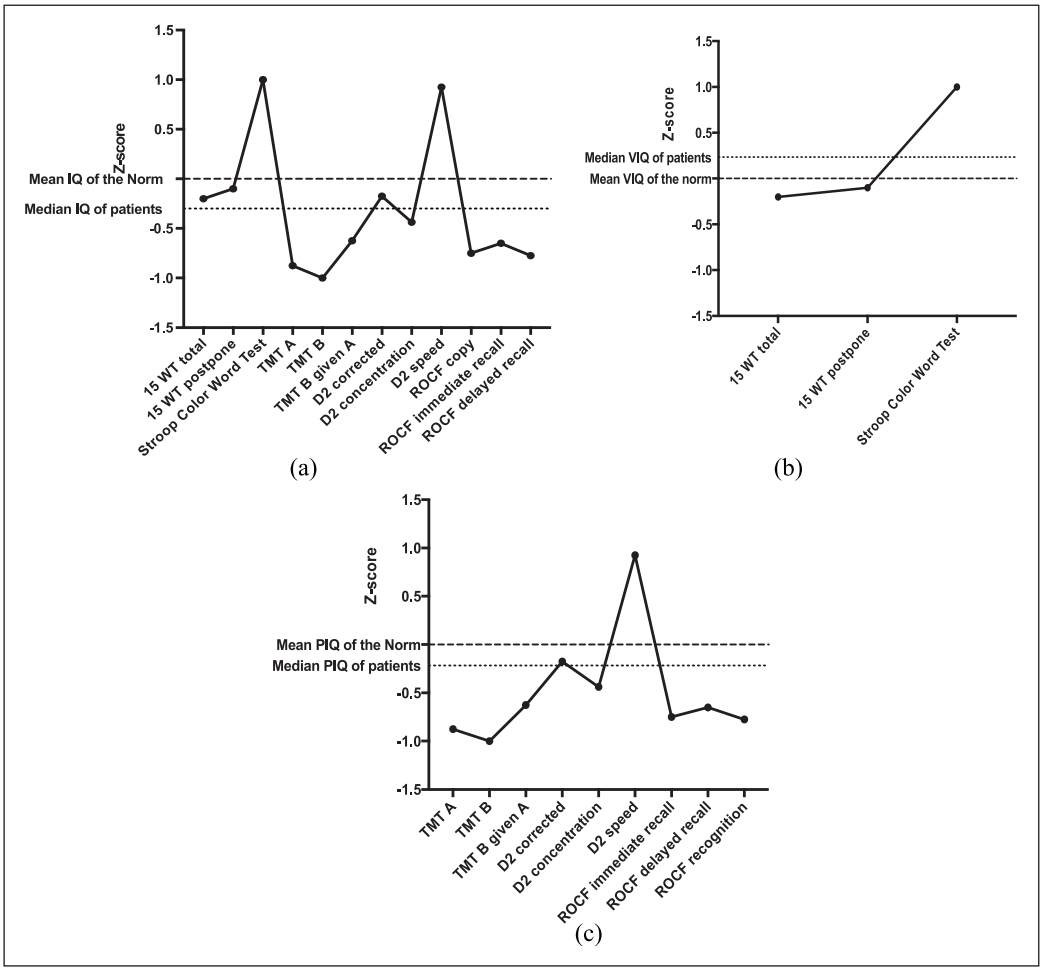

Figure 1. Overview of intelligence and neuropsychological outcome for adults with NS, adjusted for IQ. (a) Full-scale intelligence quotient (FIQ) relative to all neuropsychological tests. Results on neuropsychological tests, adjusted for median Z-score FSIQ (–0.30). (b) Verbal intelligence quotient (VIQ) relative to verbal neuropsychological tests. Results on neuropsychological tests, adjusted for median Z-scores VIQ (0.53). (c) Performance intelligence quotient (PIQ) relative to performance neuropsychological tests. Results on neuropsychological tests, adjusted for median Z-scores PIQ (–0.43). Significant difference in intelligence was found and developmental delay (lower IQ) worsens their abilities on neuropsychological test; 15 WT (total $z = –0.20$, postpone $z = –0.10$), SCWT ($z = 1.0$), TMT A/B (TMT A: $z = –0.88$; TMT B: $z = –1.00$; TMT B given A: $z = –0.63$), D2 (corrected $z = –0.18$; concentration $z = –0.44$; speed $z = 0.93$), ROCF (immediate recall $z = –0.75$; delayed recall $z = –0.65$; recognition $z = –0.78$). Neuropsychological measures of the young age-groups were only available for one child, so this score could not be combined.

by informant-report, Adult Behavior Checklist (ABCL). Adults also completed the Adult Self Report (ASR) (Achenbach, 1991; Achenbach and Rescorla, 2000, 2003). Depression in children was assessed with Children's Depression Inventory 2 (CDI-2), self-report and parent version (Kovacs, 2012) and for adults, the Beck's Depression Inventory (BDI-II-NL) was used (Van der Does, 2002). Self-esteem in children was assessed with the Dutch version of Harter's Self-Perception Profile for Children (SPP-C) by Veerman et al. (1997) and in adults with the

Table 1. Biographical characteristics of patients with NS.

Age	*N* = 12	Mean age (range)
Child	4	6.5 (3–9)
Adult	8	31.9 (21–46)
Gender	5 male/7 female	42%/58%
Marital status patient		
Unmarried, no partner	8	
Unmarried, permanent partner, not living together	1	
Married or living together	2	
Living conditions		
With parents or another care-taker	4 child/4 adult	
Living independent	3	
Daily activity		
Attending school	5	
Job	4	
Combination school and job	1	
Unemployment benefits	2	
Working hours		
Fulltime	4	
Part time	1	
Educational attainment patient		
Special education	2	
Primary education	1	
Lower	1	
Average	1	
Higher	4	
Scientific/professional	1	
Limited in career choice	5	
Special education	3	
Double a class	3	
Sick leave		
More than colleagues/peers	3	
Reason sick leave		
NS the only reason	5	

NS: Netherton syndrome.

subscale Self-esteem of the Dutch Personality Questionnaire—2 Revised (DPQ-2R) by Barelds et al. (2014). Emotional functioning in adults was furthermore assessed by two scales of the DPQ-2R: Neuroticism and Social Inadequacy (Barelds et al., 2014).

HR-QoL in children was assessed with the Child Health Questionnaire-self/parent version

Table 2. Illness-related physical or social consequences and appearance related difficulties for patients with NS.

	Patient reports ($N = 9$)	Parent reports ($N = 11$)
Learning and other problems school/work	9	
Concentration problems	5	4
Often ill due to infections	3	3
Squamae	7	7
Allergies	3	7
Fatique	4	5
Body temperature	8	8
Itching	8	9
Pain	9	7
Physical limitations	4	5
Emotional complains		4
Difficulties to sustain working/school hours		
Never	2	
Sometimes (1×/3 months)	2	
Often (>1×/3 months)	2	
Limited to go on vacation	3	8
Limited to stay/sleep else besides home	6	7
Limited to join club/association	3	4
Limited to sport	4	7
Limited in hobby's/leisure time	4	3
Limited in social context	4	6
Limited starting a (sexual) relationships	7	7
Limited in education	1	5
Limited in profession	2	6
Limitation living on your own	3	4
Limited in getting/raising children	4	7
Limited regarding nutrition	5	5
Feeling at disadvantage due to NS		
Strong related to NS	1	2
Quite related to NS	4	5
Unrelated to NS	4	4
Wish for psychological counseling	6	7
Patients worries about themselves or parents worries about patient (due to NS)	8	10
Length growth relating to peers		
Shorter	6	9
Seriousness NS, now		
Very	8	11
Visibility skin disease, now		
Very	9	11

Table 2. (Continued)

	Patient reports ($N = 9$)	Parent reports ($N = 11$)
Do you mind?		
Very	6	10
What do you think of your or your child's appearance		
Good	3	3
Not good, not bad	5	3
Not good	1	5
Satisfaction appearance self or child (not at all (0)–very much (10))		
<6	2	3
>6	7	7
Worries appearance self or child (not at all (0)–very much (10))		
<6	4	5
>6	4	5
Been bullied/offended/excluded or worries about it	6	6
Burden of staring/comments/being watched	7	8

NS: Netherton syndrome.

Table 3. Attachment and family limitations for patients with NS and their parents.

	Patient reports ($N = 9$)	Parent reports ($N = 11$)
How nice to be hold/cuddled, to hold/hug patient (not nice at all (0)–very nice (10))		
<6 (less than score 6)	1	
>6 (above score 6)	8	11
How often been held/cuddled (never (0)–very often (10))		
<6 (less than score 6)	1	
>6 (above score 6)	8	11
Attachment (not at all (0)–very much (10))		
<6 (less than score 6)	3	
>6 (above score 6)	6	11
Chance attachment		
Yes	7	6
Different attachment due to NS		
Yes	6	8
Protective		
Yes	6	9

(Continued)

Table 3. (Continued)

	Patient reports (*N* = 9)	Parent reports (*N* = 11)
Burden family live		
Big		9
By patient impossible for one of the parents to do paid work		
NS is the only reason		2
Parents less career opportunities		
For both, less opportunities		3
Patient needs more attention than other children at home		
More		8
Additional financial costs		8
No further family planning because of NS		4

NS: Netherton syndrome.

Table 4. Health-related quality of life in patients; results on self-reports of adults with NS (SF-36) and on parents-reports regarding their children with NS (CHQ-PF-50).

	Patients Median (SD)	Norm Mean (SD)
SF-36 (18–85 years)	*N* = 8	*N* = 1063
Physical functioning (PF)	85.0 (11.3)	81.9 (23.2)
Social functioning (SF)	93.5 (19.8)	86.9 (20.5)
Role limitations due to physical functioning (RP)	100 (48.0)	79.4 (35.5)
Role limitations due to emotional problems (RE)	100 (35.4)	84.1 (32.2)
General mental health (MH)	62.0 (10.1)	76.8 (18.4)
Vitality (VI)	42.5 (11.8)	67.4 (19.9)
Bodily pain (BP)	62.0 (22.0)	79.5 (25.6)
General health perceptions (GH)	52.50 (8.1)	72.7 (22.7)
CHQ-PF-50 (4–17 years)	*N* = 3	*N* = 353
PF	94.44 (17.9)	99.1 (4.3)
Role functioning: emotional/behavior (REB)	100.00 (25.7)	97.7 (7.2)
Role functioning: physical (RP)	100.00 (0.0)	95.8 (15.6)
BP	50.00 (20.0)	85.7 917.2)
General behavior (GB)	83.3 (12.8)	78.5 (13.1)
Mental health (MH)	75.00 (16.07)	81.4 (12.1)
Self-esteem (SE)	25.00 (14.6)	79.2 (11.0)
GH	60.00 (11.7)	82.9 (13.4)
Parental impact: emotional (PE)	50.00 (25.5)	86.3 (15.2)
Parental impact: time (PT)	100.00 (19.2)	94.0 (13.0)
Family activities (FA)	79.17 (22.9)	91.5 (11.9)
Family cohesion (FC)	30.00 (17.3)	72.2 (19.4)

NS: Netherton syndrome; CHQ-PF-50: Child Health Questionnaire-parent form-50; SF-36: Short Form Health Survey-36. Low scores <70 imply worse level of functioning quality of life.
Scores on the SF-36 and CHQ-PF50 scale "change in health" and summery scores are not presented since individual normative data were not available for these scales.

Table 5. Self, informant, and parent-reported executive functions (BRIEF-A/BRIEF).

	Patients *T*-score	Patients Median (SD)	Norm Mean (SD)
BRIEF-A self-report		*N* = 8	*N* = 1600
Behavioral regulation index (BRI)	*T* = 47	42.00 (5.7)	44.71 (9.6)
Metacognition index (MI)	*T* = 48	56.00 (16.8)	57.97 (12.2)
Global executive composite (GEC)	*T* = 47	97.50 (22.0)	102.7 (20.4)
BRIEF-A informant-report		*N* = 8	*N* = 1082
BRI	*T* = 46	38.50 (10.3)	44.55 (11.6)
MI	*T* = 44	50.50 (18.5)	59.67 (15.9)
GEC	*T* = 45	94.00 (24.1)	104.22 (25.6)
BRIEF parent-report		*N* = 3	*N* = 770
BRI	*T* = 57	45.22 (11.3)	55.00 (6.5)
MI	*T* = 42	78.60 (17.5)	64.00 (21.7)
GBC	*T* = 47	124.13 (26.0)	116.00 (27.5)

BRIEF: Behavior Rating Inventory of Executive Functioning; *T*-score: a score based on a normal distribution with an average of 50 and a standard deviation of 10.
Higher scores implicate worse executive functioning *T* > 60–65.
BRIEF-P young age-groups were only available for one child, so this score could not be combined.

(CHQ-CF-87/Child Health Questionnaire-Parent Form-50 (CHQ-PF-50)) (Raat, 1998; Raat et al., 2002) and in adults with the Short Form Health Survey (Short Form Health Survey-36 (SF-36)) by Ware and Sherbourne (1992). Evaluation of executive functions in children was reported with Behavior Rating Inventory of Executive Functioning Questionnaires—Parent Version (BRIEF/BRIEF-P) (Smidts and Huizinga, 2009; Van der Heijden et al., 2013). For adults, the BRIEF-A self- and informant-report version was used (Roth et al., 2005).

Patients and parents (regarding their child) rated satisfaction and worries about appearance on a linear analog scale (0 = not at all, 10 = very much), satisfaction and frequency of being held or cuddled (0 = not nice, 10 = very nice/0 = never, 10 = very often), and satisfaction of attachment/bonding (0 = not at all, 10 = very much) (for overview assessment tools and psychometric properties, see Appendix 1).

Statistical analysis

As to categorical variables, frequencies, and continuous data, means/SDs or median/interquartile ranges (IQRs) were represented. To be able to compare performance on the intelligence and neuropsychological tests, scores were compared with normative data and converted into Z-scores (the number of standard deviations from the mean a data point is). Median Z-scores of intellectual functioning were compared with median Z-scores of neuropsychological functioning. Z-scores above zero were favorable outcomes. Neuropsychological tests were corrected for age, education, and gender.

Due to the small sample size, it was not possible to test the statistical significance by one sample *t*-test between patient group and norm group on neuropsychological tests. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS 20.0).

Results

Sample description

Of the 17 eligible patients (long before this study started, two children (siblings) died due to NS, in the first year of their live) from the Dutch cohort, 12 patients and their parents participated in the study. Of the five non-participants, one 40 years old patient died due to NS complications in the

period of the start of the study. Three other adult patients and one child's parent refused to participate on emotional grounds ($N=3$, too stressful/confronting) or on practical reasons ($N=1$, distance to hospital/work). Of the remaining 12 families, 4 children (3–9 years old), 8 adults (21–46 years old), and their 12 parents (one parent or couple) participated.

Clinical manifestations, psychological outcomes

One child accomplished the complete neuropsychological tests. Of this child, the intelligence had been tested with a WISC-III recently (<2 year) and questionnaires and interviews (self and parents) were completed. Parents of two other children indicated that this was too difficult or stressful for their child and that one child lived abroad. For these remaining three children, parents provided data regarding psychosocial functioning ($n=3$, questionnaires; $n=2$, interviews). All eight adult patients completed the neuropsychological tests and questionnaires and interviews were also completed by all eight adults and their parents.

Biographical characteristics

Five of eight adult patients were still living with their parents (Table 1). Three adults had a partnership/marital status and one had children (without NS). All patients participated in regular daily activities, including school attendance, a paid job, a combination of both or voluntary work. Two adults had partly or full unemployment benefit, due to physical/mental problems. Apart from regular hospital check-ups (four times a year), no extra sick leave was reported. Three of 11 patients attended special education and 5 patients doubled a class at school. Regarding occupational status, three of five had low skilled or middle-class jobs.

Neuropsychological functioning

Of the child that completed the neuropsychological tests, the results on the Intelligence Quotient (IQ) scales showed a disharmonic profile with significant discrepancy between Verbal Intelligence Quotient (VIQ; average range) and Performance Intelligence Quotient (PIQ; borderline range). The Processing Speed Index (PSI) and Verbal Comprehension Index fell in the average range and the perceptual organization index fell in the borderline range. The neuropsychological profile showed problems on visuo-spatial memory (ROCF) and executive functioning (TMT).

Overall, the eight adults with NS scored, compared with norms, in the average range on almost all intelligence scales, VIQ: 108.00, PIQ: 93.50, Full-Scale Intelligence Quotient (FSIQ): 95.50, working memory index (WMI): 97.00, except on PSI: 85.00 (borderline range). In our sample, seven of nine patients (78%) showed a disharmonic profile with significant discrepancy between VIQ and PIQ. In five patients, in favor of VIQ.

After adjustment for their scores on intellectual functioning (FSIQ, VIQ, PIQ), patients with NS performed 1 SD score better in comparison with norms on alternated attention (EF; SCWT) and visual scanning speed (D2—speed) (Figure 1(a) to (c)). The performances on visual attention (EF; TMT A,B/B-A), short- and long-term visuo-spatial memory (ROCF-immediate/delayed recall/recognition) were lower (between ¾ to 1 SD score lower) compared with norms (Figure 1(a) and (c)). On selective/sustained attention (D2—corrected/concentration) and short- and long-term verbal memory (15 WT—total/postpone) performances were also lower (i.e. ¼ to ½ SD lower) compared to norms (Figure 1(a) to (c)).

Emotional and behavioral problems

The median scores of adults on the ASR lay above the 85th percentile (P) on somatic complaints scale and on internalizing problems. Compared with normative data, adults reported relatively high scores (P79–81) on anxious/depressed scales and attention problems. According to the adult informant-reports (ABCL), high scores (P72–84) were reported

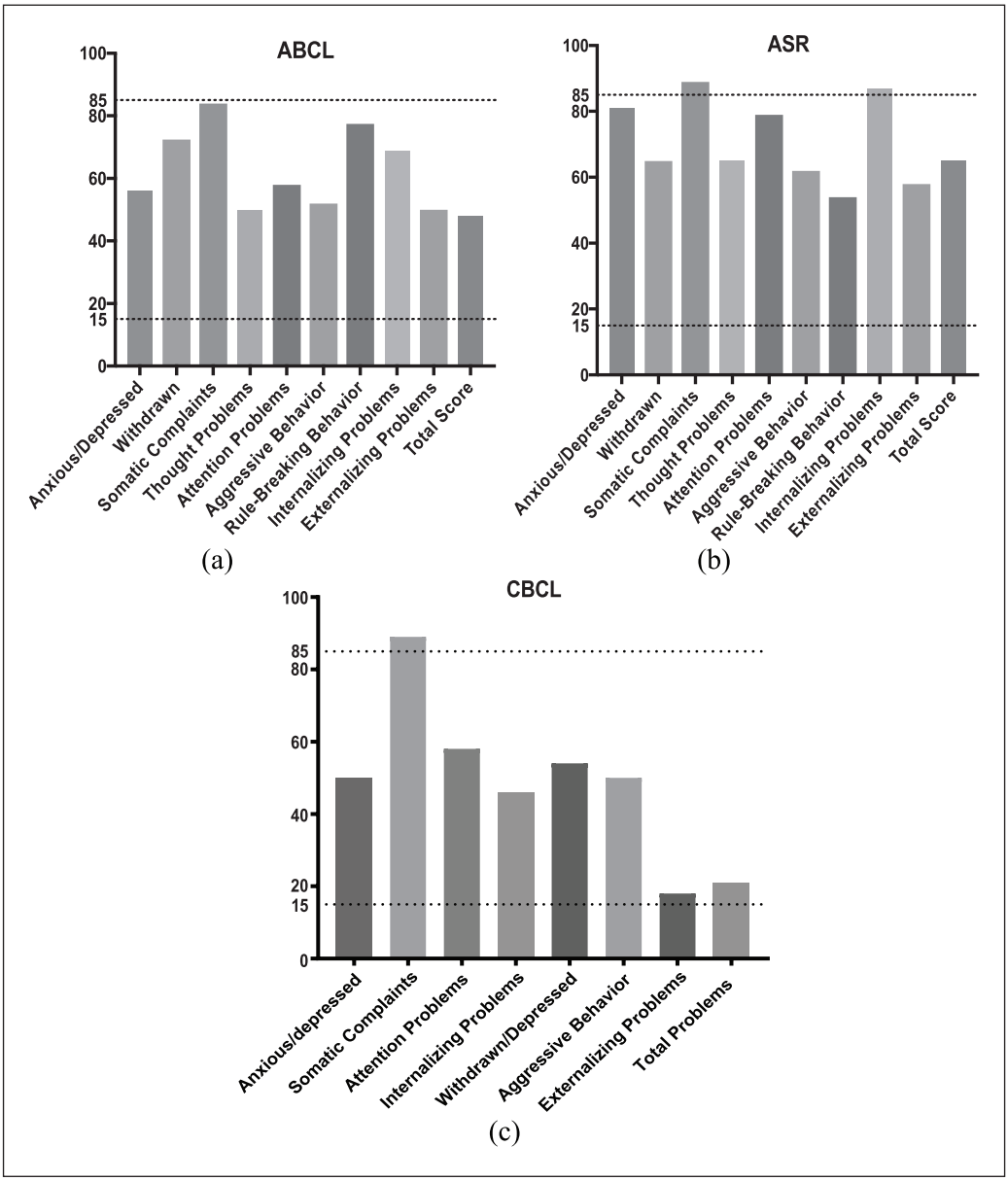

Figure 2. Emotional and behavioral functioning. (a) Results median percentile scores on the adult informant-reports (ABCL). (b) Results of median percentile scores on the self-report of adults with NS (ASR). (c) Results median percentile scores parent-reports regarding their children with NS (CBCL). Percentile scores of 85 and above indicate unfavorable outcomes.

on somatic complaints, rule-breaking behavior, and withdrawn scales. Compared with normative data parents of children with NS reported on the CBCL, relatively high problem score $P > 85$, on somatic complains scale (Figure 2).

Illness-related physical or social consequences for patients and parents

Illness-related restrictions were reported for learning and concentration problems at school, pain, itch, body temperature, squamae, impaired growth. Social consequences were experienced as to starting a (sexual) relationship, staying elsewhere, and regarding nutrition. Parents perceived their children as being limited due to NS by itching, body temperature, squamae, allergies, and pain. They felt their child was limited regarding social functioning (Table 2). Adults and parents (regarding their children) reported worries and being at disadvantage in life due to NS. As to appearance-related difficulties, patients and parents (regarding their children) reported the skin disease as serious and very visible, which they found very difficult. They rated the appearance as "not good." Patients and parents reported a favorable satisfaction score and unfavorable scores on worries about appearance. Patients and parents mentioned bullying, teasing, being excluded by peers, or the fear of being excluded. Both patients and parents experienced a burden by unpleasant remarks, staring, being ignored. Most patients (6 of 8) and parents (7 of 12) reported a wish for psychological counseling to cope with their skin disease. Patients/parents highlighted subjects such as, the outside world, self-esteem, acceptance, emotional and social consequences, and family situation.

The disease-specific burden for family life consisted of having to pay extra attention to their child with NS, financial cost incurred by illness and fewer career opportunities (Table 3). Four parents refrained from further offspring due to genetic risk. Of the seven families with more children than only the patient, four of them talked about the burden for brothers and sisters, because the disease always took priority over the siblings' needs. Parents indicated being too protective, due to fear/worries, constant care, reactions from the outside world, concerns of opportunities in life. Adults reported also protective parenting styles of their parents. As to attachment/bonding (Table 3), patients and parents reported a strong relationship, explained by the many skin contact due to comprehensive skin therapy and the conversation that took place at that time. Their relation became stronger over the years because of the illness and fear of parents they might lose their child in the first years of life. Patients and parents reported that they hold/cuddled mutually to a satisfactory extent and the attachment/bonding was satisfactory.

HR-QoL, emotional, and social functioning

Compared with norms, adults with NS reported relatively worse functioning on the HR-QoL scales (Table 4; SF-36): vitality (eight of eight), general health perceptions (seven of eight), bodily pain (six of eight), and general mental health (seven of eight). Parents of children with NS reported relatively worse functioning on HR-QoL scales (Table 4; CHQ-PF-50): bodily pain (two of three), self-esteem (three of three), change in health (two of three), emotional parental impact (three of three) and family cohesion (three of three).

On the DPQ-2R, three of eight adults reported unfavorable scores on the scale self-esteem, four of eight on neuroticism (depression-anxiety), and four of eight on social inadequacy (shyness–social avoidance) compared with normative data (Figure 3). For one child, an unfavorable self-esteem was found (SSP-C: lower scores on scales global self-worth, physical appearance, and behavioral conduct compared to the norm). One adult suffered from a clinical depression and two parents reported mild complaints of depression by the child, as shown by the BDI and CDI outcomes (Figure 4).

Executive functioning

The scores on the BRIEF-A self and informant-report for adults and the BRIEF parent report for children were comparable to normative data, favorable, on all scales (T scores < 60) (Table 5).

Discussion

In this first study concerning neuropsychological and psychosocial outcomes in children and

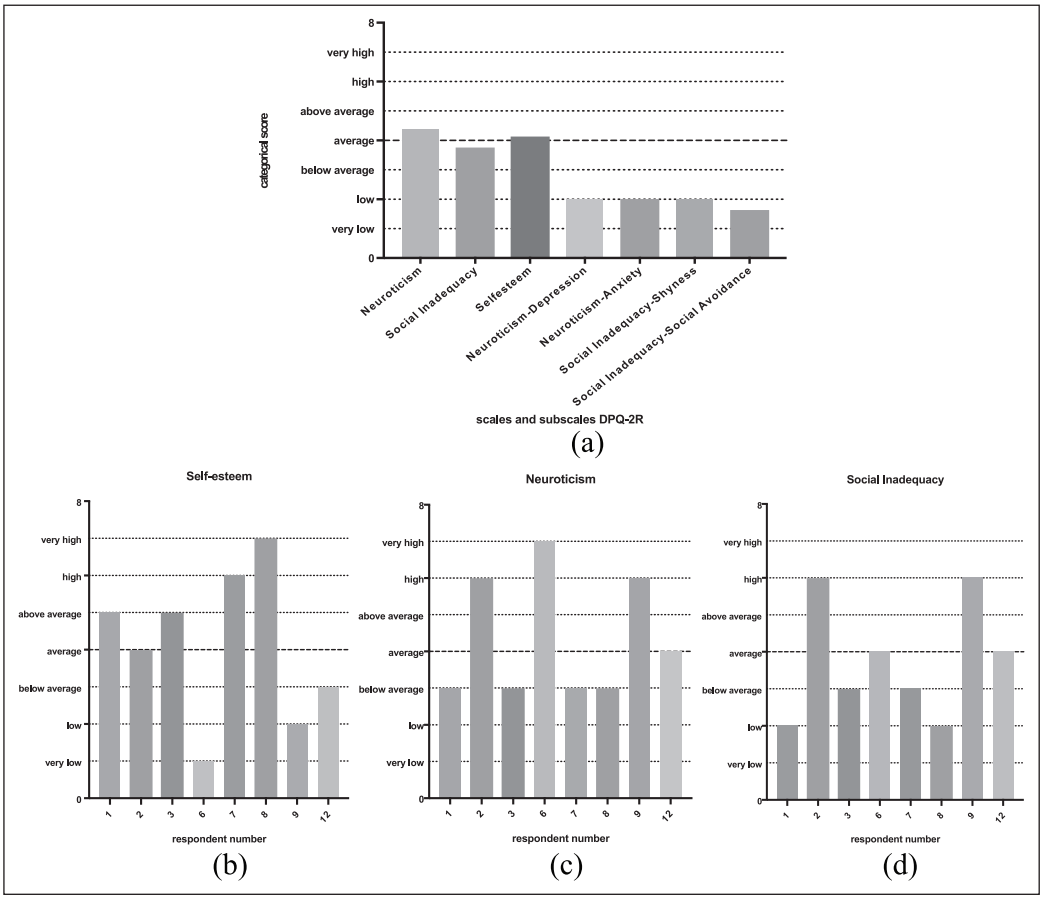

Figure 3. Dutch Personality Questionnaire (DPQ-2R). (a) Results on self-reports of adult patients. (b) Results on subscale Self-esteem. A low score on Self-esteem scale (positive attitude toward work, flexibility and being energetic and self-controlled) is unfavorable. (c) Results on subscale Neuroticism. A high score on Neuroticism (feelings of stress, depression, unstableness, and insecurity). (d) Results on subscale Social Inadequacy. A high score on social inadequacy (closed attitude, timid) indicates unfavorable outcomes.

adults with NS and their parents, substantial problems on neuropsychological functioning, HR-QoL, and illness-appearance-related aspects were found. Almost all parents suffered from a serious impact on family life due to lifestyle changes because of NS. Substantial emotional problems and a broad array of negative social consequences were found in patients with NS and parents. This supports our hypothesis that substantial neuropsychological and psychosocial problems are found related to NS or the severe skin symptoms, for patients and their families. Since this is the first psychological study in this field, we cannot compare our findings with previous studies. We know from the literature that similar psychological burdens have been found in patients and their families with other chronic skin diseases (Brown et al., 2013; Nguyen et al., 2016).

On biographical outcomes, impairments were found. The majority (five of eight adults) did not yet live independently and did not have a partner relationship. Due to the intensive and time-consuming care that parents had to give, patients

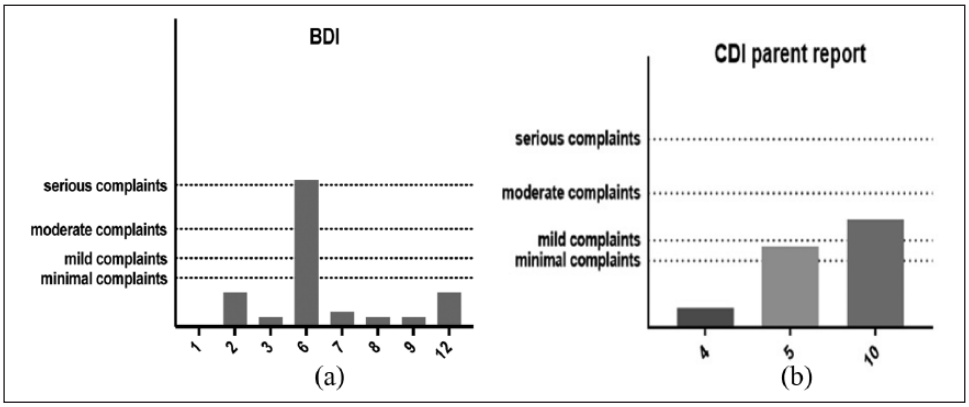

Figure 4. Depression Inventory (BDI, CDI). (a) Results of self-report of adult with NS. (b) Results on parent-reports regarding their children with NS. A high score is unfavorable.
CDI—child report is only available for one child, so this score could not be combined.

with NS can be overprotected by their family, making the individualization and separation process more difficult. In the literature, delay in gaining autonomy and independence has been described for patients with chronic diseases (Opic et al., 2016; Zomer et al., 2012). Moreover, due to the (fluctuating) visibility, patients with NS may feel less attractive, which may hamper their self-esteem, social contacts, and participation in peer groups. This hamper has also been described in the literature on psoriasis, a visible chronic skin disease (Kouris et al., 2016; Nazik et al., 2017; Nguyen et al., 2016).

Overall, our results regarding special education and doubling a grade are in line with the Dutch normative data based on De staat van onderwijs (2015) and Centraal Bureau voor Statistiek, 2014 (percentage of children attending special education: 5%; doubling a grade: 27%). Scores on the intelligence test in adults with NS fell in the average range, except for processing visual information (below average).

On neuropsychological tests, adults with NS, overall, performed well on alternated attention (EF) and visual scanning speed. However, problems were found on selective/sustained attention, visual attention (EF), visuo-spatial and verbal memory. The neurocognitive problems may be explained by pathophysiological processes of NS (itch, vitality, pain, inflammations, infections), with possible consequences of insufficient benefit from education due to the burden of NS symptoms. This may have hampered their performance during testing. In the literature, this is also described in other pediatric chronic diseases as diabetes, congenital heart defects/disease, and sickle cell disease (Compas et al., 2017). Moreover, these problems were found in adult patients with NS. This indicates the importance to follow the neurocognitive capabilities of young children with NS.

Disharmonic intelligence profiles were remarkable in our cohort of NS. Significant discrepancies, mostly in favor of VIQ, were found by adults and child. In the normal (child) population, disharmonic profiles occur in 25 percent, whereas in our sample this was 78 percent. This suggests implications for daily living, school, and working abilities. If there are stronger verbal possibilities than performance possibilities, problems may occur such as insufficiently balanced visual-constructive information processing ("seeing and then doing"), difficulty with practical tasks, not being able to oversee tasks at school, and work and organizing their own emotions/behavior (Emmen, 2012; Van der Bergh, 2017). Disharmonic intelligence profiles and neurocognitive problems are known in other samples of pediatric conditions (asthma, prematurity, lysosomal-metabolic

disease, meningococcal septic shock) defined by Ebbink et al. (2016), Irani et al. (2017), Larroque et al. (2008), and Vermunt et al. (2009) and some of those conditions (e.g. metabolic and septic shock) have shown apparent abnormalities in the white matter of the brain (Ebbink et al., 2016; Vermunt et al., 2009). Little is known about the underlying mechanisms which can explain disharmonic intelligence profiles in pediatric conditions, making it difficult to compare outcomes with the present findings.

This study shows unfavorable outcome on somatic complaints for adults and children with NS. For adults, we also found internalizing problems. Adults and children's parents reported unfavorable HR-QoL. Previous investigations, showed similar unfavorable outcomes (Beattie and Lewis-Jones, 2006; Dures et al., 2001; Lewis-Jones and Finlay, 1995; Shobaili 2010; Verhoeven et al., 2007). They reported worries about pain, general health, vitality, parental impact, and cohesion. Emotional or social problems were reported by adults (four of eight: fear-depression and social inadequacy. Lowered self-esteem due to the (fluctuating) visibility was demonstrated in the interview only. This may reflect an underappreciated source of psychological consequences in patients with NS by socially desirable responses on questionnaires. We found in the interviews, appearance-related problems by adults which influenced self-esteem. Parents reported also problems as to social life for their child, due to appearance-related conditions of NS. They indicated, loneliness, not being understood by the environment, social exclusion, fearful anticipation, struggling with appearance. The inconveniences, fear, and the sadness of stigmatization due to the visibility of the skin disease (unpleasant remarks, being teased/bullied, social exclusion) were shared by most. The same was evident in earlier research into appearance-related conditions (Lovegrove and Rumsey, 2005; Magin et al., 2008; Rumsey Harcourt, 2004; Tuckman, 2017). These sequelae of NS hamper children and adults in their emotions, behavior, self-esteem, and social contacts.

Regarding outcomes for parents themselves, they reported NS was a burden for their family life. The family impact suggested life-style changes in several areas, financial stresses, social impact, family activities, and personal strain. Some talked about the burden for siblings of patients with NS, the impact of NS interfered with giving adequate attention to siblings. These findings are in line with previous study (Beattie and Lewis-Jones, 2006; Shobaili, 2010). Protective parenthood due to NS may also be a beneficial factor, with positive outcomes on attachment/bonding. A strong patient–parent relationship was reported in the interviews, parents, and adults mentioned that skin contact through emollient therapy also had positive effect, due to the intensity and the close connection.

Considering the above, despite protective factors, patients and parents had to fight for "being more than just an affected skin." Despite its small sample size, this is, to our knowledge, worldwide the largest reported cohort of NS in one country and the first psychological study in this field. A unique feature of this study was trying to involve all Dutch patients, with a broad clinical spectrum of NS (and parents) for neuropsychological assessment and interviewing. A multi-informant approach was used. Due to the small sample size, we cannot draw conclusion on relation between severity of the skin disease and psychological consequences. To get more insight by gathering more data in a larger sample, we have set up a database linked to a personal health record of the patient (DermHome: https://www.huidhuis.nl). Further research should be done, ideally with inclusion NS patients internationally. In addition, siblings were not involved, so their feelings on the NS burden on family life is missing. Finally, skin disease- and appearance-related questionnaires should be developed and validated.

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Appendix 1

Semi-structured Rotterdam quality of life interview	Parents	Patient Age 6–17	Patient Age >18	Psychometric properties
Biographical characteristics NS-related questions regarding current physical problems (fatigue, pain, itching, etc.), psychosocial functioning (living, work, school/ study, leisure time, etc.), appearance-related difficulties, attachment, and limitations	Parents interview	Patient interview Age 6–17	Patient interview Age >18	None
Tests				
Intellectual functioning		WISC-III-NL Age 6–16	WAIS-VI-NL Age 16–85	WISC-III α .94 (FSIQ); .92 (VIQ); .87 (PIQ); *r* .92 (FSIQ); .88 (VIQ); .89 (PIQ) WAIS-VI α .97 (FSIQ); .96 (VIQ); .93 (PIQ); *r* .95 (FSIQ); .93 (VIQ); .89 (PIQ)
Memory Verbal Visual		15 WT ROCF	15 WT ROCF	15 WT α .86–.90; *r* .70 ROCF *r* .76 (immediate recall); .89 (delayed recall); .87 (recognition)

(Continued)

Appendix 1. (Continued)

Semi-structured Rotterdam quality of life interview	Parents	Patient Age 6–17	Patient Age >18	Psychometric properties
Executive functions	BRIEF-P/BRIEF (questionnaire)	SCWT Age > 8.0 TMT BRIEF	SCWT Age > 8.0 TMT BRIEF-A	SCWT α .81–.89 TMT *r* .75 (A); .85 (B); .74 (B-A) BRIEF-P α .95; *r* .88 BRIEF α. .95–.96 (BRI/MI/GEC); *r* .84–.95 (BRI/MI/GEC) BRIEF-A α .93–.96 (BRI/MI/GEC); *r* .93–.94 (BRI/MI/GEC)
Attention		D2 Processing speed index (WISC-III-NL)	D2 Processing speed index (WISC-III-NL/WAIS-III-NL)	D2 α .83–.97; *r* .33–.83
Questionnaires				
Health-related quality of life	CHQ PF 50 Age 5–18	CHQ CF 87 Age 5–18	SF-36	CHQ PF 50 α mean .72; *r* .37–.84 CHQ CF 87 α mean .80 SF-36 α .71–.92; *r* .40–.75
Emotional and social functioning		SSP-C	DPQ-2R	SSP-C α .74; *r* .77 DPQ-2R α .74–.93; *r* .86–96

Appendix 1. (Continued)

Semi-structured Rotterdam quality of life interview	Parents	Patient Age 6–17	Patient Age >18	Psychometric properties
Emotional and behavioral problems	CBCL parent Age 1,5–5/6–18 ABCL informant Age 18–59		ASR Age 18–59	CBCL 1,5–5 α .66–.95; *r* mean .85 CBCL 6–18 α .66–.98; *r* mean .74–.89 ABCL α .85; *r* mean .86 ASR α .83; *r* mean .88
Depression	CDI-parent	CDI-2	BDI-II-NL	CDI-2 α .59–.88; *r* .51–.66 CDI-2 parent α .72–.87 BDI-II-NL α .88; *r* .82
Satisfaction and worries about appearance	Regarding their child, on a linear analog scale (0 = not at all, 10 = very much)	On a linear analog scale (0 = not at all, 10 = very much)	On a linear analog scale (0 = not at all, 10 = very much)	None
Frequency of being held or cuddled	(0 = not nice, 10 = very nice/0 = never, 10 = very often)	(0 = not nice, 10 = very nice/0 = never, 10 = very often)	(0 = not nice, 10 = very nice/0 = never, 10 = very often)	
Satisfaction of attachment/bonding	(0 = not at all, 10 = very much)	(0 = not at all, 10 = very much)	(0 = not at all, 10 = very much)	

α: Cronbach's alpha; *r*: test–retest reliability.