Influence of Learning Disabilities on the Tumour Predisposition Syndrome NF1 – Survey from Adult Patients' Perspective

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Abstract. *Aim: To analyze psychosocial burdens associated with neurofibromatosis type-1 (NF1) phenotype – visible symptoms, medical complications, learning disabilities (LD) – from patients' perspective with focus on LD. Patients and Methods: A survey of 228 adult patients with NF1 was carried-out. Symptoms to estimate disease severity and visibility, and learning disability were assessed. Outcome parameters were social situation and psychosocial aspects. Results: Social situation and psychosocial aspects differed depending on NF1 phenotype. Patients with LD (n=55) were less frequently in a partnership (p=0.005) or had children (p=0.015) than those without (n=132). They also reported a higher frequency of depression (p=0.019) and sensitivity to stress (p<0.001) and more uncertainty regarding NF1-associated symptoms. These differences were significant when adjusting for disease severity and self-perceived disease visibility. Conclusion: Beside the psychosocial needs of patients with LD with NF1, medical management of this sub-group should include doctor–patient communication in easy language to compensate for patients' lack of knowledge about symptoms associated with cancer.*

Neurofibromatosis type-1 (NF1) is a rare genetic cancer predisposition syndrome with a prevalence of 1 in 3,000 (1, 2). The disorder is inherited as an autosomal dominant trait but it also occurs sporadically in 50% of the affected individuals. NF1 is caused by mutations on chromosome 17q11.2 (3), where the *NF1* gene was found in 1990 (4). The product of this gene, neurofibromin, is involved in rat sarcoma (Ras) GTPase activation. Ras GTPase down-regulates the Ras protein family involved in cellular signal transduction associated with cell proliferation and differentiation. A lack of neurofibromin may lead to decreased inhibitory control of cell growth, consequently increasing the risk for tumour genesis (5). A decreased regulation of the RAS pathway is also suspected to lead to decreased synaptic plasticity and, as a consequence, deficits in learning and memory, resulting in a variety of learning disabilities (5, 6).

Patients with NF1 are characterized by the development of multiple benign and malignant tumours in the peripheral and central nervous system. Patients with high tumour load and increased growth rate are at risk of malignant peripheral nerve sheath tumours (MPNST) (7). MPNST is the main cause of reduced life expectancy in patients with NF1. These tumours usually arise from pre-existing plexiform neurofibromas and are associated with a five-year survival rate of 42% (8). Patients at risk for MPNST need close clinical follow-up observation. They also have to be able to perceive subtle physical changes and then associate these with cancer risk. About 50% of patients with NF1 have directly visible/palpable or internal plexiform neurofibromas. Even if plexiform neurofibromas do not turn malignant, they may grow extensively and cause significant neurological deficits and disfigurements (9). Surgical removals are difficult and in many cases risky and only partially possible. In contrast to large (30%) or disfiguring facial plexiform neurofibromas (3-5%), which are usually congenital (9), cutaneous and subcutaneous neurofibromas affect almost all adults, and they increase in number with age (10). Disease-associated appearance (skin manifestations and skeletal deformations) has a negative impact on psychological health (11), on quality of life (12, 13) and on the body image (14) in adult patients.

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In the last ten years, studies have shown a negative effect of the NF1 phenotype on the quality of life in adults (12,13). These studies focused on the effect of clinical complications and disease-associated appearance, but they did not address the cognitive and behavioural phenotype of NF1 in adults. Learning disabilities, specific cognitive deficits, and attention deficit hyperactivity disorders (ADHD) are a considerable part of the NF1 phenotype and the most common complications in children with NF1, affecting 30-60% (15-17). In children, they cause social interaction problems (18, 19) and impaired school performance (20). Longitudinal studies in patients show that NF1-associated cognitive deficits can persist through adulthood (21). NF1-related cognitive deficits such as visual–spatial skills, memory, executive functioning and attention problems are still present in adults (22, 23). The anticipated effect of a learning disability and attention deficits in adult patients with NF1 has only been reported in few studies. A qualitative interview study in a small cohort of adults with NF1 revealed that male patients with a learning disability are prone to social withdrawal and have less experience in relationships and sexual contacts (24). In addition, adults with NF1 with average intelligence and ADHD reported less overall life satisfaction and an elevated emotionality (highly sensitive and nervous) than adults with NF1 only (25).

How the NF1 phenotype affects the lives of adults, especially under consideration of learning disabilities, has to our knowledge not been evaluated in a larger sample. Knowledge of how a learning disability affects the lives of adults with NF1 is important for providing them with adequate support and care. In the present study, we questioned adult patients with NF1 through self-report of their social situation and psychosocial aspects in a questionnaire. Group comparisons, *e.g.* between those who reported being diagnosed with a learning disability and those without, were performed to explore the effect of learning disabilities on social situations and psychosocial aspects, while also taking disease severity and perceived visibility into account.

Patients and Methods

Procedure and patients. This study was part of a cross-sectional survey on healthcare utilization and satisfaction of adult patients with NF1 (26). Between March and June 2009, adult patients with NF1 were recruited to the study at lay meetings, at the NF Centre of the University Medical Center Hamburg-Eppendorf, *via* local patient groups and by mailing to members of lay organizations. Patients older than 18 years who gave informed consent returned their completed questionnaire anonymously. NF1 diagnosis according to NIH consensus (27) was confirmed by a specialist in those patients recruited by the NF Center (n=32). Patients recruited at the lay meeting (n=75), in local patient groups (n=75) or by mail (n=46) self-reported that a physician confirmed their NF1 diagnosis. Study inclusion was limited to patients who, according to their responses, had a medically verified diagnosis of NF1. The questionnaire was written in simple language. Patients with problems filling in the questionnaire by themselves were able to get assistance, which was then specifically declared. A contact person was available at site for patients recruited at the lay meeting and at the NF Centre to answer questions on how to fill in the questionnaire. A phone number and e-mail address for a contact person were provided for those patients who received the questionnaire by mail. Patients with significant difficulties filling in the questionnaire were excluded from the analysis. A total of 228 adult patients with NF1 were included. However, due to missing values, valid cases for each analysis were usually less than 228. The study protocol was approved by the Ethics Commission of the State Medical Association of Hamburg, Germany (no. PV3106).

Measures. The questionnaire covered the following aspects. All data were based on patients' perception and knowledge regarding their condition.

Disease-related medical severity, perceived disease visibility, and learning disabilities: Disease-related symptoms perceived by the patient and diagnostic data (imparted to patients by their physicians) were assessed. Disease severity was classified using a dichotomized Riccardi scale (28). Symptoms reported in the questionnaire allowed severity classification. Low severity was defined as Riccardi scale 1 or 2 without significant NF1-related compromise of health; high severity (Riccardi scale 3 or 4) was associated with significant NF1-related compromise of health. Intellectual and psychological functioning was excluded from the severity rating to avoid a confounding effect between a learning disability and medical severity.

To assess perceived disease visibility, a scale with four items was developed to assess if patients thought that their disease was visible to others when fully dressed. The scale measured patients' subjectively perceived disease visibility on a scale from 0 (no perceived disease visibility) to 4 (disease is perceived as highly visible to others). Reliability of the scale (0-4) of disease visibility with four items was considered good, with a Cronbachs alpha of 0.85. For the analysis, we dichotomized the visibility scale to compare patients who perceived their NF1 to be highly visible to those who perceive their NF1 at most moderately visible to others.

Learning disabilities were assessed by asking the patients to declare if they had been diagnosed with a learning disability by a specialist. Furthermore, the participants were asked to state if they currently had learning problems on a five-point Likert scale from 0 (no learning problems) to 4 (severe learning problems). Learning disabilities are by definition based upon academic failure, defined by academic achievement of two standard deviations below average, lasting longer than two years. This also includes low intelligence, IQ<85, and specific learning disabilities with normal IQ (29).

Outcome parameters: Social situation: Questions referred to age, sex, level of education, current occupational situation, household net income, partnership, biological children, living arrangement, and if they had been sexually engaged.

Psychosocial aspects: Lifetime depression and ADHD diagnosis were assessed by questions in which patients were asked if they had been diagnosed by medical professionals. Self-perceived measures of sensitivity to stress were rated on a five-point Likert scale from 0 (no sensitivity to stress) to 4 (high sensitivity to stress).

Statistical analysis. Clinical characteristics and demographics were described with frequency analysis. The scales for learning problems

Table I. *Demographics and phenotype characteristics based on patients' reports.*

	Total (n=228)			
Demographics	Number (n)	Valid (%)	Missing values	
Partnership: yes	110	48.7	2	
Biological children: yes	81	37.9	14	
Education: primary school[1]	65	30.0	11	
Household net income <2000€	142	67.0	17	
Clinical features				Unsure* n (%)
Cafe au lait spots: yes	212	96.4	4	4 (1.8)
Neurofibromas: yes	203	95.3	8	7 (3.2)
Freckling: yes	136	76.8	16	35 (16.5)
Plexiform neurofibroma: yes	108	72.5	37	42 (22.0)
Scoliosis: yes	121	63.4	12	25 (11.6)
Hypertension: yes	70	32.6	5	8 (3.6)
Optic pathway glioma: yes	25	13.3	13	27 (12.6)
Short stature: yes	19	8.3	22	26 (12.6)
Brain tumor: yes	19	9.4	12	13 (6.0)
Malignant tumor: yes	16	8.3	25	11 (5.4)
Pseudarthrosis in childhood: yes	4	2.4	40	18 (9.6)
Associated features				
Attention deficit: yes	47	24.6	9	28 (12.8)
Learning disability: yes	55	25.5	21	29 (13.4)
Disease-related characteristics[2]				
Disease severity: high	150	65.8	-	
Perceived disease visibility: high	122	53.5	-	

[1]Nine years of education or less; [2]assessed from symptoms and items of perceived disease visibility reported by participants; *additional category, labelled as missing values for the analysis. Unsure, participants reported not being certain of the diagnosis.

and sensitivity to stress were dichotomized as present or not present for analysis. Firstly, differences between those with a diagnosed learning disability and those without were analyzed regarding outcome parameters. Secondly, the patients were divided into groups of low *vs*. high disease severity, as well as low *vs*. high disease visibility, and the differences between those with and without learning disabilities within these groups were analyzed. Dichotomous parameters were compared between two groups using Chi square test (χ^2). Effect-size for Chi square test was determined by Cramer's phi where 0.10, 0.30 and 0.50 represent small, medium and large effect sizes. Differences with a probability of a type I (alpha) error of 0.05 or less were considered statistically significant in all analyses. Due to the explorative character of the study, a correction of the alpha error inflation arising from multiple testing was not performed (30). All statistical analyses were carried out using PAWS statistics 18. for Windows, IBM®, Germany.

Results

Sample description. A total of 228 adults with NF1, aged between 18 and 79 years (mean age±SD=43.8±13.3 years) participated in the study. There were more women (n=140, 61.7%) than men (n=87, 38.3%). Disease severity and perceived visibility score were estimated in all patients. High disease severity was found in 150 (65.8%) adults and 122 (53.5%) perceived their disease as being highly visible to others. Fifty-five (29.4%) out of 187 adults (valid responses) reported having a learning disability; additionally, 29 (13.4%) adults reported having learning problems but were not sure if they had received this diagnosis. Ninety-six percent (n=53) of those who reported having a learning disability also confirmed current having learning problems. Altogether, 149 (66.8%, 5 missing values) reported having current learning problems.

Table I shows NF1 demographics and clinical features of our sample. Patients with higher disease severity also perceived their disease as being more visible (χ^2=21.94, df=1, p<0.001) and reported a higher frequency of a learning disabilities (χ^2=8.84, df=1, p=0.003). There was no association between a learning disability and disease visibility (χ^2=0.86, df=1, p=0.35).

Uncertainty regarding clinical features of NF1. A high frequency of uncertainty regarding some typical clinical features

of NF1 was expressed by the patients (Table I). We analyzed if the uncertainty was associated with a learning disability. We found that uncertainty regarding plexiform neurofibromas (χ^2=5.97, df=2, p=0.05), pseudarthrosis (χ^2=7.10, df=2, p=0.03), brain tumour (χ^2=16.36, df=2, p<0.001), optic glioma (χ^2=9.82, df=2, p=0.007), malignant tumour (χ^2=9.36, df=2, p=0.009) was associated with learning disability.

Social situation – influence of learning disabilities. Social situation differed between patients with and without learning disability. Patients with a learning disability were less frequently in a partnership (χ^2=7.90, df=1, p=0.005), fewer had been sexually engaged (χ^2=5.23, df=1, p=0.022), fewer had biological children (χ^2=5.91, df=1, p=0.015) and a larger number still lived with their parents (χ^2=6.16, df=1, p=0.013) than those without a learning disability. There was no age difference between the groups with and without a learning disability (42.2±14.0 years *vs*. 44.4±13.0 years, p<0.47). Those with learning disabilities reported lower education levels than those without learning disabilities (χ^2=15.21, df=1, p<0.001) but there were no differences regarding working situation (χ^2=0.41, df=1, p=0.52) and household net income (χ^2=2.79, df=1, p=0.10) between groups.

Psychosocial aspects. Attention deficit disorder (χ^2=350.0, df=1, p<0.001) and depression (χ^2=5.47, df=1, p<0.019) was significantly more often diagnosed in patients with a learning disability compared to those without. Patients with learning disabilities were also more sensitive to stress than those without (χ^2=17.71, df=1, p<0.001).

Effect of disease severity and visibility. To test if the group differences between those with and without learning disabilities were not better explained by disease severity and disease visibility, we compared those with and without learning disabilities within those with low *vs*. high disease severity and those with low and high disease visibility respectively.

Within those with high disease severity, we found no learning disability-related differences in social situation parameters except for the level of educational (χ^2=8.12, df=1, p=0.004; see Table II) between groups. However, those with a learning disability reported a higher frequency of attention deficit disorder (χ^2=24.75, df=1, p<0.001) and depression (χ^2=4.10, df=1, p=0.043) compared to those without. In contrast, there were differences between those with and without a learning disability regarding social situation parameters within those with low disease severity (Table II). Here, none of the patients with a learning disability were in a partnership (χ^2=12.94, df=1, p<0.001), none had biological children (χ^2=7.81, df=1, p=0.005) and more lived with their parents (χ^2=4.18, df=1, p=0.041) compared to those without a learning disability. Patients with a learning disability reported more sensitivity to stress than those without a learning disability, regardless of disease severity (within low disease severity χ^2=5.86, df=1, p=0.016, within high disease severity χ^2=7.49, df=1, p=0.006).

Within those who perceived their NF1 as being highly visible, we found no learning disability-related differences in social situation parameters, except for the level of education (χ^2=60.02, df=1, p=0.014; see Table III) between groups. However, those with a learning disability reported a higher frequency of attention deficit disorder (χ^2=17.78, df=1, p<0.001) compared to those without. In contrast there were differences between those with and without learning disabilities regarding social situation within those with low disease severity (see Table III). None of the patients with a learning disability had biological children (χ^2=13.70, df=1, p=0.001), fewer were in a partnership (χ^2=9.85, df=1, p=0.002) or had been sexually engaged (χ^2=5.60, df=1, p=0.018) compared to those without a learning disability. Those with a learning disability also reported a higher frequency of attention deficit disorders (χ^2=16.86, df=1, p<0.001) than those without. Patients with a learning disability reported more sensitivity to stress than those without a learning disability, regardless of disease visibility (within low disease visibility χ^2=6.21, df=1, p=0.013, within high disease visibility χ^2=10.44, df=1, p=0.006)

Discussion

This study shows a high frequency of learning disabilities in adult patients with NF1. There was a high uncertainty in those with a leaning disability regarding their clinical manifestations, *e.g*. plexiform neurofibromas (22% unsure). When patients are unsure of their clinical manifestations in the frame of this complex disease there may be a higher risk of failure to recognize subtle changes and symptoms which may indicate tumour growth and malignant transformation. *NF1* is primarily a tumour-suppressor gene disorder and therefore medical care mostly focuses on medical complications and associated physical manifestations, such as tumour burden and other disease complications (*e.g*. cancer). This study analysed how learning disabilities, as part of the NF1 phenotype, affected social life and psychosocial aspects (depression and sensitivity to stress) from the point of view of adult patients with NF1. The results showed that adults with NF1 and learning disabilities were more likely to be without a partner and less likely to start their own family. They were also more often living with their parents. These differences between those with and without learning disabilities were present while comparing patients with less severe medical phenotype (Tables II and III). There were higher frequencies of depression and sensitivity to stress in those with a learning disability compared to those without, independent of disease severity and perceived disease visibility. This indicates that those with learning disabilities have fewer abilities to cope with NF1 and with everyday stresses.

Table II. *Group comparisons concerning social situation and psychosocial aspects between patients with and without learning disability (LD) with regard to disease severity.*

	Low disease severity n=78 (60*)			High disease severity n=150 (125*)				
	Without LD n=51 n (%)[a]	With LD n=9 n (%)[a]	*P*[c]	Without LD n=81 Φ[d]	With LD n=44 n (%)[a]	n (%)[a]	*P*[c]	Φ[d]
Social situation								
Partnership: yes	33 (64.7)	0 (0.0)	≤0.001	0.46	42 (51.9)	18 (40.9)	0.242	0.11
Sexually engaged: yes	44 (89.8)	6 (66.7)	0.064	0.24	63 (79.7)	31 (68.9)	0.175	0.12
Children: yes	26 (53.1)	0 (0.0)	0.006	0.37	28 (36.4)	11 (27.5)	0.335	0.09
Living with parents: yes	7 (14.9)	4 (44.4)	0.041	0.27	9 (12.0)	11 (25.6)	0.058	0.06
Highest education:								
primary school[b]	10 (21.3)	6 (75.0)	0.002	0.42	18 (22.8)	21 (47.7)	0.004	0.26
Working: yes	35 (70.0)	6 (66.7)	0.842	0.03	41 (50.6)	22 (50.0)	0.947	0.01
Household net income: <2000€	20 (41.7)	4 (66.7)	0.389	0.16	59 (74.7)	33 (76.7)	0.801	0.02
Psychosocial aspects								
Attention deficit: yes	3 (6.3)	1 (16.7)	0.385	0.34	12 (16.0)	26 (60.5)	0.001	0.44
Depression: yes	10 (21.7)	2 (22.2)	0.974	0.10	27 (35.5)	23 (54.8)	0.043	0.18
Sensitive to stress: yes	10 (21.3)	5 (62.5)	0.016	0.33	35 (50.0)	32 (76.2)	0.006	0.26

*With valid LD diagnosis. [a]Percentage valid; [b]primary school=9 years of education, secondary school=more than 9 years of education; [c]by Chi^2 test or Fisher test; [d]Cramer's ϕ effect size for Chi^2 test.

Table III. *Group comparisons concerning social situation and psychosocial aspects between patients with and without learning disability (LD) with regard to subjectively perceived disease visibility.*

	Low visibility n=106 (88*)			High visibility n=122 (98*)				
	Without LD n=65 n (%)[a]	With LD n=23 n (%)[a]	*P*[c]	Without LD n=67 Φ[d]	With LD n=31 n (%)[a]	n (%)[a]	*P*[c]	Φ[d]
Social situation								
Partnership: yes	39 (60.0)	5 (21.7)	0.002	0.34	36 (53.7)	13 (43.3)	0.344	0.10
Sexually engaged: yes	38 (60.3)	5 (22.7)	0.002	0.25	30 (46.2)	9 (30.0)	0.137	0.10
Children: yes	28 (43.8)	0 (0.0)	0.001	0.40	26 (41.9)	11 (40.7)	0.916	0.01
Living with parents: yes	9 (15.0)	7 (30.4)	0.128	0.18	7 (11.3)	8 (27.6)	0.070	0.21
Highest education: primary school[b]	49 (80.3)	10 (45.5)	0.002	0.34	16 (24.6)	15 (50.0)	0.014	0.25
Working: yes	40 (61.5)	14 (60.9)	0.955	0.01	36 (54.5)	14 (46.7)	0.474	0.07
Household net income: <2000€	30 (48.4)	5 (25.0)	0.066	0.20	47 (72.3)	22 (75.9)	0.719	0.04
Psychosocial aspects								
Attention deficit: yes	7 (11.3)	11 (55.0)	0.001	0.45	8 (13.1)	16 (55.2)	0.001	0.42
Depression: yes	16 (25.8)	9 (40.9)	0.183	0.16	21 (35.0)	16. (55.2)	0.070	0.18
Sensitive to stress	20 (33.3)	13 (65.0)	0.013	0.28	25 (43.9)	24 (80.0)	0.001	0.35

*With valid LD diagnosis. [a]Percentage valid; [b]primary school=9 years of education, secondary school=more than 9 years of education; [c]by Chi^2 test or Fisher test; [d]Cramer's ϕ effect size for Chi^2 test.

For treating physicians and most researchers, disease severity and disease visibility are often considered the major factors impairing quality of life and causing psychological stress in adult patients with NF1 (11-13). In children with NF1 however, there have been several reports of an impact of learning disabilities (31) and behavioural problems (*e.g.* ADHD) (32) on quality of life. Similarly to this study, Noll *et al*. explored the effect of the NF1 phenotype (general, appearance and neurological disease severity) on social and emotional functioning. The authors concluded that children with typical neurological problems of NF1 (*e.g.* attention and learning problems) have a high risk for future behavioural, social, and emotional problems (33). This indicates that learning disabilities and attention deficits may have a long-term impact on adult life achievements and emotional functioning. Based upon reports of young adults with NF1,

low self-confidence is often related to impaired school achievements and bullying or visible symptoms of NF1. In this qualitative study, almost all participants reported having learning and attention problems, and those with late diagnoses later (in late adolescence or adult life) experienced more problems at work (34).

There was a high association between learning disabilities and ADHD in our sample (55% reported co-morbid learning disabilities and ADHD). ADHD in adults with NF1 is associated with emotional instability and lower life satisfaction (general health, self-satisfaction, sexuality, and family) (25). It is advised that adults should be tested for both diagnoses if they report learning and attention problems or have difficulties managing adult life expectations.

The study design did not allow confirmation of a learning disability diagnosis and other clinical parameters by a specialist, which limits the generalization of our results. The diagnosis was assessed by asking patients if they had been diagnosed with a learning disability by a specialist. It is possible that patients, especially those with a learning disability, have problems recalling this information accurately. The frequency of a learning disability (29.4%) in this sample is probably an underestimation. Twenty-nine adult patients reported having learning problems but did not confirm being diagnosed with a learning disability because of uncertainty. This means that they may not yet have been officially diagnosed. This selected sample is biased against patients with severe cognitive problems because of the exclusion of patients with difficulties completing the questionnaire. Altogether 66.8% of the patients reported having some kind of problem in learning, which indicates that learning problems are an issue in adults with NF1. Patient reports as a source for medical data for a severity rating have previously been questioned as being unreliable (13). Patients also seem to perceive their disease as more severe when they present more cosmetic features (13, 35). This limits the interpretation because all data were based upon patient reports. However, a different way of assessing disease severity was used in this study. Patients were not asked to assess their disease severity, they were asked for NF1-specific symptoms with significant compromise of health, and estimated disease severity was based upon the reported symptoms. Nonetheless, more studies on learning disabilities in adults with NF1 are needed. These should include clinical confirmation of learning disability and a combination of self- and third-party reports on social life situation and potential burdens.

The findings of this study emphasize the importance of different treatment options in adults depending on clinical severity, perceived disease visibility, and learning disability. In particular, adult patients with NF1 with a learning disability need a combination of medical and psychosocial care. These patients need specific medical information regarding NF1 manifestations, the importance of follow-up examinations and careful medical consultation regarding the subtle symptoms indicating tumour growth and malignancy. These consultations should be performed in simple language. Learning disabilities in adults are a challenge for neurologists and psychiatrists because there is no single effective drug or medical treatment available for this subgroup of patients (36). Furthermore, systematic screening for psychosocial burden should be part of the care of adults with NF1. Patients with a learning disability may be in need of additional interventions of psychosocial support, which should be defined by neurologist, psychiatrists and psychologists. Close cooperation among medical professionals, psychologists and social workers is essential for reducing subjective burden and improving the quality of life in adults with NF1.

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