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Neuropsychological discovery in neurofibromatosis 1 family associated with a novel pathogenic intronic variant in NF1

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Abstract

Background: Neurofibromatosis 1 (NF1) is a common autosomal disorder, caused by mutation of the tumor suppressor gene chromosome 17q11.2 in humans. Neurocognitive difficulties are common in patients with NF1. The aim of the study was reported, how novel variant of gene mutations correlations with cognitive disabilities, such as ADD JA ADHD of the same NF1 family.

Case presentation: A family with NF1 disease, a 15-year-old girl with NF1and her 43-year-old mother with NF1, were genetically and neuropsychologically investigated.

The girl and her mother were diagnosed with NF1 at the same time. Due to neuropsychological difficulties the neuropsychological assessment was done. Attention-Deficit Disorder (ADD) was diagnosed in the 15-year-old girl and Attention Deficit Hyperactivity Disorder (ADHD) was diagnosed in her 43-year-old mother. Sequence analysis of the patient's cultured lymphocyte cDNA sample using an RNA-based long-range PCR and sequencing identified aberrant inclusion of 86 base pairs (r.8113_8114ins8113+1_8113+85 p.(ser2705SerfsTer3). The variant c.8113+86A>G was confirmed in the cDNA of the NF1 gene. This is causative and clinically important heterozygous pathogenic variant according to ACMG classification system (ACMG Class 5).

Conclusion: Cognitive disabilities, such as ADD and ADHD, can vary in the members of the same NF1 family with pathogenic and novel variant of c.8113+86A>G. Early diagnosis of both NF1 and cognitive disabilities followed by an adequate treatment plan, including collaboration between different medical specialists, are essential in treating NF1 patients, which enables better quality of life patients with NF1.

Keywords: Neurofibromatosis 1; Neuropsychology; Intellectual disability.

Background

Neurofibromatosis 1 (NF1) is a common autosomal neurodevelopmental disorder, caused by mutation of the tumor suppressor gene chromosome 17q11.2 in humans [1]. The most common manifestations of NF1 are in the skin, bone, and nervous system. Despite marked phenotype expression variability, up to 70% have learning problems [2,3]. Neuropsychological development and impairment of NF1 plays an important role in NF1 disease and treatment plan, but unfortunately this is rarely reported [4-6].

Patients with NF1 commonly present low intellectual functioning. Hyman, et al. 2005 reported that patients scored 90 QI points in average and had a high incidence of intellectual disability (-7%). Visuospatial failure plays an important role in the development of cognition [7]. Furthermore, NF1 patients often have problems with working memory, inhibitory control, motor control, set-shifting and language [8]. Cognitive failure seems to be stable in patients with NF1 [8].

The aim of our study was to describe the neurophysiological assessment and treatment of patients from different generations of the same family and highlight the importance of the collaboration between different medical specialists in complete treatment of patients with Neurofibromatosis 1.

Case Presentation

Family description

The 15-year daughter was diagnosed with NF1 with plexiform neurofibroma in paravertebral nodus, in the posterolateral division, which is near the nervous system, at the Department of Clinical Genetics, Turku University Hospital, Turku. Axillary and inguinal freckling and café au lait -spots in skin were detected in the girl at the age of 9 years. There is a soft tissue lump on her neck, and freckles near it. MRI scan revealed the lump as a plexiform neurofibroma [9]. These are typical skin manifestations in patients with NF1.

The 43-year-old mother was diagnosed with Neurofibromatosis 1 (NF1), at the Department of Clinical Genetics, Turku University Hospital, Turku, Finland. She had typical NF1 skin manifestations, but no neurofibromatosis was found. She worked with children and suspected that she had ADHD (attention deficit hyperactivity disorder).

The father of the mother was diagnosed with NF1 at the age of 48 years based on his symptoms: café au lait sports, neurofibromas on skin as well as plexiform neurofibroma in the right upper arm. At the age of 74 years an MRI scan showed diffusion thickness of spinal nerves in the spinal canal and extraspinal neurofibromas. No operation was required. He was treated for GIST at the age of 65 years, when three synchronous GISTs were removed from ileum, jejunum and stomach. All three GIST were primary and were low risk tumors and KIT positive.

NF1 was clinically diagnosed, but a genetic cause was not found by next generation sequencing. Therefore, running mRNA analysis was arranged by the Department of Clinical Genetics, Turku University

Hospital, Turku, Finland,

The mother suspected that she and her daughter had neuropsychological problems due to NF1 and requested a neuropsychological consultation. The father did not mention experiencing work affecting neuropsychological symptoms and did not participate in the neuropsychological investigation.

Neuropsychological investigation methods in the daughter (Patient A)

Evaluation methods: Observation, interview, and cognitive tests; parts of Wechsler Intelligence Scale for Children-Fourth Edition WISC-IV [10-12]. Continuous Performance Task (CPT3) [13], Trail Making Test (TMT a+b) [14], self-evaluation about attentiveness and operation management and BRIEF- inquiry filled out by guardians, ADHD-inquiry (DuPaul), feedback from school.

Neuropsychological investigation methods in the mother (Patient B)

Methods: observation, interview, and cognitive tests; parts of The Wechsler Adult Intelligence Scale-IV (WAIS-IV) [10-12], parts of The Wechsler Memory Scale, Third Edition (WMS-III) [15], The Benton Visual Retention Test (version C), Continuous performance task (CPT3) [13], Trail Making Test (TMT a+b) [14], Stroop test (Stroop), 3D-copy, Cerad-clock, Rey-Osterreith Complex Figure Test (ROCFT)[16].

Neuropsychological findings in the daughter (Patient A)

The patient has been assessed twice with neuropsychological and speech-language pathology assessments. The primary problem is exhaustion, which also influences her studies as she tires easily during the school day compared to her peers. She has difficulties in executive function: starting and maintaining activities when the activities are not personally motivating, or the subject is difficult. This has become more obvious during remote school (due to COVID-19). The patient has not been diagnosed with learning difficulties in academic skills. The neuropsychological assessment was made at the Department of Neurology, Turku University Hospital, Turku, Finland. At this she was diagnosed with ADD.

Verbal reasoning and concept formation was assessed to be on the average level of her age group, and descriptive vocabulary was slightly over the average level of her age group. Visual perception and reasoning assessed with the visuospatial construction test and the matrix reasoning test were assessed to be on the average level of her age group. Working memory assessed with the digit span test was assessed to be slightly over the average level of her age group. Processing speed was on the average level of her age group.

As a summary it was assessed that ADD related symptoms in attention were most likely causing tiredness and problems in executive functions in her everyday life. Intensified support and special arrangements in school were recommended due to problems with attention and executive functions.

Neuropsychological investigation in the mother (Patient B)

The mother does not have learning difficulties in academic skills except in mathematics. The mother has difficulties with visual-spatial performance. This causes challenges, for example in finding her parked

car in a parking lot. The neuropsychological assessment was made at the Department of Neurology, Turku University Hospital, Turku, Finland. ADHD had been diagnosed earlier.

There was a strong indication of inattentiveness and some indication of impulsivity in a computer-based attention test. In all other tests of attention her performance was assessed to be in the normal range. Visual perception and reasoning assessed with the visuospatial construction test was slightly below the average of her age group. Processing speed was also slightly below the average of her age group.

As a summary it was noted that the cognitive symptoms observed in the neuropsychological assessment were converging with the everyday symptoms, she had noticed herself. Neuropsychological rehabilitation was recommended to help her gain strategies and aid for the everyday life problems related to her cognitive symptoms.

Results of neurocognitive follow-up

The 15-year-old girl with NF1 was diagnosed with ADD. The primary problems were exhaustion and attentiveness disturbance, which may be caused by ADD. However, her conscientiousness and average level of cognitive capability may have disguised these disruptions. The cognitive level of the girl was good and age consistent (Table 1).

The 43-year-old woman with NF1 was diagnosed with ADHD. The most important neuropsychological observations were problems with attention, visual perception and reasoning, and processing speed (Table 1).

Result of genetic studies

The 15-year-old girl and the 43-year-old mother were diagnosed with Neurofibromatosis 1 at the Department of Clinical Genetics, Turku University Hospital, Turku, Finland. Either neurofibromatosis Next-Generation Sequencing (NGS) panel or MLPA-analysis of copy number variation were unable to find a pathogenic variant. However, the pathogenic variant was observed at RNA level. Sequence analysis of the patient's cultured lymphocyte cDNA sample using an RNA-based long-range PCR and sequencing identified aberrant inclusion of 86 base pairs (r.8113_8114ins8113+1_8113+85 p.(ser2705SerfsTer3)). The additional 86 base pairs cause a shift in the reading frame of the codons in the mRNA, which leads to an alteration in the amino acid sequence at protein translation. The variant c.8113+86A>G was confirmed in the cDNA of the NF1 gene. This is causative and clinically important heterozygous pathogenic variant according to ACMG classification system (ACMG Class 5) [17]. No other variants of clinical relevance were detected in the NF1 transcript (Table 1).

Table 1:

	Patient A (14 years)	Patient B (43 years)
Main reasons for referral to neuropsychological assessment	Tiredness and problems with attentions and concentration	Challenges in everyday life; difficulty with visual perception and coordination
NF1 diagnosis	Yes	Yes
NF1 complications	No	No
Development delay (early history)	No	No
Cognitive assessment (WISC-IV/WAIS-IV)	Average level of age group	Slightly below average on visuospatial reasoning. Slightly below average on processing speed
Attention and executive function	ADD diagnosed	ADHD diagnosed. Inattentiveness and impulsivity in CPT3 Some problems in executive functions such as planning
Memory	Working memory slightly over average	No significant problems with learning or memory
Language assessment EXLANG	No significant problems with language functions	No significant problems with language functions
Psychiatric diagnosis	ADD	ADHD
Medication		Methylphenidate
Nonpharmacological treatment		Neuropsychological rehabilitation

Discussion and Conclusion

Our case report presented different neuropsychological impairments in the same family. As both the mother and daughter had clear neuropsychological challenges investigation was done. The girl with NF1 had mild cognitive difficulties and ADD. Her mother with NF1 also had mild cognitive difficulties and ADHD. According to previous studies cognitive difficulties are common in patients with NF1 [2,9,18,19] and this study supports results of previous studies. Patients with NF1 often have difficulties with learning and attention [18]. A previous study also found evidence of impairment in all academic areas including word reading, reading comprehension, mathematics, and spelling in comparison to siblings and other unaffected children [19]. According to previous studies, in addition to deficits in attention visual-spatial performance and social competence are most commonly seen in NF1 patients, but also problems with executive function, and memory are frequently seen [3,19,20].

NF1 patients with learning disabilities have more depression, sensitivity to stress and uncertainty on NF1 symptoms [21-24]. In this case the family view is that neuropsychological difficulties clearly affect negatively everyday life. The mother said that she and her daughter have some of these difficulties and that is why she asked for investigations. The mother has difficulties in visual observations, for example she does not remember people's faces well. Patients with NF1 have been described to have difficulties in academic skills, but there have been no such difficulties in this family, except in mathematics in the mother. Patients with NF1 have more fatigue than the population on average and this is also the case in this family. The mother has an ADHD diagnosis. The mother described that acting is difficult in a non-structured environment or external activity. In everyday life this has manifested as a difficulty in finishing activities, including cleaning and other household chores. Earlier in life studying of larger projects was also difficult. Now at university studies seem to be going well, after learning to schedule and structure the work. A recently

published study found that NF1 significantly undermines economic well-being and causes economic inequality, and that patients with NF1 have lower incomes [25]. The Finnish social security system partially compensates for the loss of income of patients, as NF1 disease affected the income from work more than the total income of the patients in the cohort [25].

According to our knowledge access of NF1 patients to neuropsychological investigations is limited in many hospitals. As neuropsychological investigation showed in our NF1 patient cognitive problems can be seen early in childhood. An early NF1 diagnosis and observation of neuropsychological difficulties often affiliated with NF1 are the cornerstones of good medical practice. They play a crucial role in the quality of life of patients with NF1, including family life, education, and work. NF1 children who are diagnosed early and are planned surveillance makes the detection and reaction to emerging academic problems in school and home possible [26,27].

Neuropsychiatric examinations and support measures should be arranged as soon as they become necessary, multidiscipline collaboration. The variable cognitive phenotype highlights in patients with NF1 requires that a neuropsychological assessment is carried out in childhood. Support should also be arranged for those who have been diagnosis as adults [5,21]. This necessitates extensive collaboration between different medical specialists. Specialists treating children with NF1 will need to elucidate the mechanisms underlying each child's difficulty in performing visuospatial, verbal, memory and learning, motor, executive, or attention tasks (or likely a combination of these) in order to recommend the most suitable interventions [18].

The family's pathogenic variant is c.8113+86A>G and is not yet reported in ClinVar. The additional 86 base pairs cause a shift in the reading frame of the codons in the mRNA and leads to an alteration in the amino acid sequence at protein translation. According to our knowledge this is the first described family with this mutation. This variant explains family members' NF1 symptoms. This variant is intronic variant and is exceptionally rare and is not found in control populations (gnomAD no frequency). According to ACMG classification, the identified NF1 variant in the family is pathogenic. NF1 gene is huge, intronic variants are not well identified. Running mRNA analysis was essential in finding the family mutation. Genotype-phenotype correlation in NF1 is not well understood, and phenotype with this variant has varied from café au lait spots, plexiform neurofibromas and sarcoma tumors in gastrointestinal tract to neuropsychological problems.

Declarations

Ethics approval and consent to participate: The study complies with the Declaration of Helsinki regarding the use of human samples and identifiable information. This study is a case report and informed consent was obtained from the patients regarding the use of information obtained during clinical treatment. The data analyzed in the study was from patients who had been treated at the hospital. As no new samples were required a separated ethics board permit was not required

Consent for publication: Written informed consent was obtained from the patient's legal guardian

for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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