Motor dysfunction in NF1: Mediated by attention deficit or inherent to the disorder?

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A B S T R A C T

Aim: Attention deficit and compromised motor skills are both prevalent in Neurofibromatosis type 1 (NF1), but the relationship is unclear. We investigated motor function in children with NF1 and in children with Attention Deficit/Hyperactivity Disorder (ADHD), and explored if, in patients with NF1, attention deficit influences motor performance.

Methods: Motor performance was measured using the Movement Assessment Battery for Children (M-ABC) in 71 children (26 with NF1 plus ADHD, 14 with NF1 without ADHD, and 31 with ADHD without NF1) aged 6–12 years.

Results: There was a significant effect of group on motor performance. Both NF1 groups scored below children with ADHD without NF1. Attention performance mediated motor performance in children with ADHD without NF1, but not in children with NF1.

Conclusions: Motor function is not mediated by attention performance in children with NF1. While in ADHD, attention deficit influences motor performance, motor problems in NF1 seem to be independent from attention deficit. This argues for different pathomechanisms in these two groups of developmental disorders.

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Similar to a range of other neurodevelopmental disorders, Neurofibromatosis Type 1 (NF1) is associated with impairment of motor skills.1 NF1, belonging to the so called RASopathies, is a rare autosomal-dominant genetic neurodevelopmental disorder with a worldwide incidence of 1 in 3000. It is caused by heterozygous mutations in the NF1 gene on chromosome 17q22.1 and is characterized by a specific phenotype which especially concerns skin and nervous system and tumor development. The NF1-gene product Neurofibromin (a Ras GTPase-activating protein that inactivates the cellular proto-oncogene Ras) is involved in tumor suppression and in the
regulation of synaptic plasticity. Ras hyperactivity, caused by reduced levels of neurofibromin, is strongly associated with decreased synaptic plasticity. In adults with NF1, decreased long-term-potentiation-like plasticity in primary motor cortex was demonstrated using transcranial magnetic stimulation (TMS), which was associated with impaired motor learning. Motor learning was compromised even in clinically unimpaired adults with NF1, suggesting that decreased motor plasticity is a feature inherent to the condition. Research is only beginning to shed light on the pathomechanisms leading to disturbed motor plasticity in NF1. In the murine model, GABAergic-cortical dysfunction due to a hyperactivity of the Ras pathway was suggested as a causal factor for learning deficits. Also for human patients with NF1, abnormalities in the GABA system involving GABA concentration and GABA receptor density are implied suggested as causative for neurodevelopmental synaptopathy. This hypothesis is supported by evidence for reduced frontal GABA levels and for alterations of ion channel activity. Another possible pathomechanism leading to motor deficits are Schwann cell abnormalities resulting in increased K+ signaling and, consequently, slower conduction velocities.

Motor deficits in NF1 are a burden for the patients and their families which is reflected by the large number of prescriptions for physiotherapy or occupational therapy. Impairments include hypotonia and hampered gross motor coordination and balance as well as fine motor function.

Motor impairment is also common in another distinct neurodevelopmental disorder: Attention deficit-/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric diseases in childhood (American Psychiatric association). The etiology is multifactorial, with genetic, environmental, and epigenetic factors contributing to the phenotype. Neurotransmitter dysbalance (particularly in the fronto-striatal catecholaminergic system) as well as structural differences in the brain are suspected to cause the core symptoms of inattention, hyperactivity and impulsivity. In addition, more than 50% of the children with ADHD have problems affecting gross and fine motor skills and, thus, qualify for the diagnosis of developmental coordination disorder (DCD). It is still under debate whether the motor problems in ADHD are resulting from basic neurological problems (i.e., DCD) or rather from problems in attention and executive functions.

A common neural basis for the motor problems in both groups is suggested by similar atypical findings in motor network functional connections revealed by MRI between patients with ADHD and those with DCD. On the other hand, the extent of motor abnormalities in children with ADHD was correlated with their attention problems in a recent study, suggesting also a cognitive (top-down) influence on motor skills in this group.

In addition to motor problems, attention deficit is another commonality shared by children with NF1 and children with ADHD. Being present in a major proportion of patients with NF1, problems of inattention, hyperactivity and impulsivity are severe enough to fulfill the ADHD criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in up to 50% of them. There is evidence that, similar to ADHD, the attention deficit in NF1 may be generated by a disturbance of the catecholaminergic metabolism in fronto-striatal brain structures. Recent animal studies suggest that neurofibromin deficiencies lead to reduced dopamine signaling, which might be responsible not only for impairments in learning and memory but even more so for attention problems in NF1. So far, there is only little data on the relationship of attention and motor problems in NF1. Gross motor function has been associated with executive functions, but up to now, our knowledge on the influence of attention is very limited.

In summary, NF1 patients as well as ADHD patients show motor dysfunction and attention problems, but so far there are no studies that examined the relationship between motor impairment and attention deficits in an NF1 population. Regarding the fact that both diseases — ADHD per se as well as NF1 per se — result in motor problems, it can be hypothesized the combination of the two (assuming attention deficit as an additional negative risk factor for motor dysfunction in NF1) result in more severe motor dysfunction. More specifically, we expected (H1) significantly impaired motor skills in patients with both NF1 and ADHD as compared to patients with NF1 only or ADHD only. Further, we expected (H2) a positive correlation of attention problems with motor problems in both patient groups, those with NF1 and those with ADHD.

1. Material and methods

1.1. Subjects

The cross-sectional, observational study was approved by the local ethics review board (655/2012BO1). Participants were consecutively recruited between 2013 and 2015 at the University Hospital Tübingen (Dept. Pediatric Neurology, Dept. Child and Adolescent Psychiatry and Psychotherapy). Prior to any assessment, all patients provided written parental consent and child assent for participating in the study. During the course of one day, all participants individually underwent (a) neurological examination, (b) neuropsychological assessment, and (c) motor assessment. Breaks were repeatedly offered. In parallel, parents completed questionnaires and a semi-structural interview with a psychologist. All data were registered in a pseudonymized manner in a centralized database. Inclusion criteria were: (1) NF1 diagnosis according to the diagnostic criteria of the National Institute of Health Consensus Development Conference statement and/or ADHD diagnosis according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), (2) age between 6 and 12 years, (3) intelligence quotient between 70 and 115, and (4) typical psychiatric comorbidities of NF1 and ADHD were allowed, including specific developmental disorders of speech and language, learning disorder, conduct disorder and emotional disorders. Exclusion criteria were: (1) intracranial manifestations like symptomatic optic nerve glioma, brain tumor, traumatic brain injury, stroke or hemorrhage, (2) epilepsy, (3) very preterm birth and (4) severe psychiatric disorders (e.g. autistic disorders). All 71 participants (100%) were native speakers of the German language. Fourteen patients (20%) had pure NF1 (NF1control group), 31 patients (43%) had pure ADHD (ADHDcontrol group), and 26 patients (37%) had NF1 and such profound attention problems
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