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Neuropsychological evaluation and parental assessment of behavioral and motor difficulties in children with neurofibromatosis type 1

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem disorder, with large inter and intrafamilial clinical variability and uncertain prognosis. In children with NF1 cognitive disorders, learning difficulties and behavioral problems are common.

The present study aims to establish the neuropsychological and behavioral profiles of 78 patients with NF1, aged between 5 and 18 years, and to examine the relationship between these profiles and the transmission of NF1 (sporadic vs. familial), clinical manifestations, and environmental factors.

We used several questionnaires completed by parents and neuropsychological tests.

The results confirmed specific neuropsychological disabilities in children with NF1, especially involving visuospatial and fine motor skills, learning difficulties and behavioral problems. Cognitive difficulties were significantly more frequent in patients with familial than in those with sporadic NF1. All parental questionnaires were correlated with each other, but parental reports were not associated with FSIQ, SES, school status, and clinical manifestations of the disease.

Neuropsychological tests were poorly related to parental reports of cognitive and behavioral difficulties.

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What this paper adds?

- The present study uses parental questionnaires and neuropsychological tests to establish behavioral and cognitive profile in children and adolescents with neurofibromatosis type 1 (NF1). We assess visuo-spatial and fine motor skills in the NF1, and we examine correlations between clinical manifestations, environmental factors, behavioral and neuropsychological profiles of these children. We also compare the cognitive profile of sporadic and familial transmissions of NF1.

1. Introduction

Neurofibromatosis 1 (NF1) is a common autosomal dominant disorder with a prevalence of 1 in 4000–5000, and an incidence of 1 in 2000–3000 births (Evans et al., 2010). Approximately half of NF1 cases are inherited and half are caused by sporadic *de novo* heterozygous mutation of the *NF1* gene at chromosome 17q11.2. This multisystem disorder is characterized by large inter and intrafamilial clinical variability and uncertain prognosis (Ferner, 2010). Clinical phenotype may also change substantially with age, because patients with NF1 can develop one or more multisystemic complications during their life, resulting in the characteristically high morbidity and significantly increased mortality of this disease. Common manifestations are *café au lait* macules, axillary and/or inguinal freckling, neurofibromas and Lisch nodules. The complications of NF1 involve different bodily systems such as the skin, eyes, bone, nervous system, cardiovascular system, respiratory system or gastrointestinal system (Ferner, 2010). NF1 is currently diagnosed according to the clinical criteria of the National Institute of Health Consensus Conference statement (NIH, 1988). Cognitive problems and learning difficulties are very frequent in children with NF1 and are the most common complication affecting quality of life (Hyman, Shores, & North, 2005). Patients with NF1 usually have an IQ in the low to average range, but about 6% have an intellectual disability (Ferner, Hughes, & Weinman, 1996; Hyman et al., 2005; Hyman, Shores, & North, 2006). Particular cognitive functions may be impaired (Lehtonen, Howie, Trump, & Huson, 2013; Levine, Rimrodt, Clements-Stephens, & Cutting, 2006), especially visuospatial skills (Hyman et al., 2003; Schrimsher, Billingsley, Slopis, & Moore, 2003), motor skills and coordination (Hyman et al., 2005), complex psychomotor skills (Descheemaeker, Ghesquière, Symons, Fryns, & Legius, 2005), attention (Gilboa et al., 2011; Hyman et al., 2005; North, Hyman, & Barton, 2002; Payne, Hyman, Shores, & North, 2011), and executive functions (Hyman et al., 2005; Payne et al., 2011).

Learning disabilities and behavioral problems are often reported by the parents of children with NF1 (Lehtonen et al., 2013; North et al., 1997). According to many reports, about 50% of children with NF1 have learning disabilities (Descheemaeker et al., 2005; Hyman et al., 2005), and approximately 30 to 50% meet the diagnostic criteria of attention deficit hyperactivity disorder (ADHD) (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008; Cutting & Levine, 2010; Hyman et al., 2005; Johnson, Saal, Lovell, & Schorry, 1999; Kayl & Moore, 2000; Koth, Cutting, & Denckla, 2000; Levine et al., 2006; Roy et al., 2010). ADHD is a major risk factor for poor social skills and behavioral problems in children with NF1 (Barton & North, 2004).

The diagnosis of ADHD in children with NF1 is often based on interviews and questionnaires completed by parents and teachers, such as the Conners' Parent Rating Scale (Conners, Sitarenios, Parker, & Epstein, 1998), or the Child Behavior Checklist (CBCL; Achenbach, 1991). Many children and adolescents with NF1 have clinically significant scores on various Conners' subscales measuring inattention, cognitive problems, hyperactivity, or ADHD criteria (Gilboa et al., 2011). Studies using the CBCL report similar findings (Barton & North, 2004; Dilts et al., 1996; Johnson et al., 1999; Noll et al., 2007). Children with NF1 also show clinically significant scores on the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000a, 2000b), as rated by parents and teachers (Gilboa et al., 2011; Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef, & Josman, 2014; Payne et al., 2011). However, the results of particular neuropsychological tests of attention or executive functions and parental reports of inattention/hyperactivity (Conners Third Edition-Parent, Conners, 2008) or executive functions (BRIEF) are poorly correlated (Isenberg, Templer, Gao, Titus, & Gutmann, 2012; Payne et al., 2011).

Several questionnaires, not specific to NF1, have shown that Quality of Life (QoL) is strongly affected in patients with NF1 (Graf, Landolt, Capone Mori, & Boltshauser, 2006; Oostenbrink et al., 2007; Page et al., 2006; Wolkenstein, Zeller, Revuz, Ecosse, & Leplège, 2001). QoL is worse in patients with NF1 than in those with other chronic diseases, such as asthma, because of complications, especially orthopedic manifestations, learning disabilities and plexiform neurofibromas (Wolkenstein et al., 2009). Parents are more pessimistic than patients themselves (Oostenbrink et al., 2007; Wolkenstein et al., 2009), and pessimism is less common in familial than in sporadic NF1 (Wolkenstein et al., 2009).

It remains unclear how behavioral difficulties, QoL and cognitive deficits are related in children with NF1. Furthermore, studies report inconsistent findings regarding the relationship between cognitive–behavioral difficulties, clinical manifestations and the transmission of NF1 (sporadic versus familial) (Barton & North, 2004; Ferner et al., 1996; Hyman et al., 2005; Wolkenstein et al., 2009). Here, we used questionnaires completed by the parents of children or adolescents with NF1 to evaluate cognitive and behavioral difficulties (Conners' Parent Rating Scale, CBCL, and BRIEF). We also used quality of life scales (Impact of Childhood Illness Scale, Short QoL Scale) and assessed parents' concerns about their child's learning and