

Clinical Case Rounds in Child and Adolescent Psychiatry:

Neurofibromatosis Type 1, Cognitive Impairment, and Attention Deficit Hyperactivity Disorder

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Neurofibromatosis Type 1 (NF-1) is an autosomal dominant disorder that occurs in approximately 1 out of every 3000 live births. Common physical features include café au lait spots, skinfold freckling, iris hamartomas, and the growth of benign and malignant tumors (Gutmann, 2002). The gene associated with NF-1 has been mapped to the long arm of chromosome 17 and is usually classified as a tumor suppressor gene, explaining the high frequency of benign and malignant tumours found in this disorder (North et al., 2002).

In addition to the physical manifestations of NF-1, cognitive impairment is also common (North et al., 2002). Early reports overestimated the degree and prevalence of this impairment or suggested a nonverbal learning disability profile. More rigorous studies conducted over the last 20 years suggest only a slightly increased incidence of mental retardation, intellectual abilities that are generally in the low average range but remain within one standard deviation of the normal population, and an equivalent prevalence of language and nonverbal based deficits (North et al., 1997). An increased incidence of learning disabilities is also reported, with frequencies reported to range between 30 and 65% (North et al., 1997). While a large body of literature has explored the link between intellectual/learning difficulties and NF-1, the relationship between NF-1 and attention deficit hyperactivity disorder (ADHD) has only become a focus of investigation in the last decade. The following two cases, recently assessed in our clinic, are presented to illustrate the attentional and learning concerns associated with NF-1.

Case 1

Case 1 is a 10-year-old male who was referred to the ADHD clinic for an assessment of attentional difficulties. He was diagnosed with NF-1 at the age of 5. Our clinical evaluation confirmed a diagnosis of Attention Deficit

Hyperactivity Disorder, Predominantly Inattentive Type. He met all 9 criteria for Inattention, all 3 Impulsivity criteria, and 2 out of the 6 criteria for Hyperactivity. The Conners' Parent Rating Scale revealed clear impairment in ADHD related realms, and the Conners' Teaching rating scale suggested problems with anxiety, emotional lability, and social difficulties. A psychoeducational assessment (Table 1) conducted in our clinic demonstrated that intellectual abilities were overall below the mean for the general population, but within one standard deviation. Working memory was more severely impaired. There was no discrepancy between verbal and nonverbal domains. Academic testing demonstrated low average performance on spelling and reading. Memory was also impaired, with verbal memory scores almost one standard deviation below the mean, and visual memory scores almost two standard deviations below the mean. Difficulties with fine motor and visuospatial skills were also evident.

Case 2

Case 2 is a 12-year-old male who has been followed since age 7 for a suspected diagnosis of NF-1. He was referred to our clinic at the age of 10 with depressive symptoms, difficulty focusing in class, and a decline in his academic performance. His depressive symptoms coincided with the death of a close relative and remitted with weekly psychotherapy. Ongoing difficulties at school prompted a detailed assessment.

Clinical evaluation indicated that all 9 criteria for Inattention were present; however, only 2 out of 6 criteria for Hyperactivity-Impulsivity

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Table 1: Case comparison on standard scores of selected measures of intellectual abilities and academic achievement

	Case 1	Case 2
Intellectual Abilities		
WISC IV-Full Scale IQ	88	114
WISC IV-Verbal Comprehension	93	99
WISC IV-Perceptual Reasoning	92	127
WISC IV-Working Memory	77	104
WISC IV-Processing Speed	103	112
Academic Achievement		
WRAT-Reading	86	104
WRAT-Spelling	85	110
WRAT - Mathematics	98	111
WRAML - Verbal Memory	85	102
WRAML - Visual Memory	72	116
Beery - Visual Motor Integration	86	111

Note: WISC-IV = Wechsler Intelligence Scale etc, WRAT = Wide Range Achievement Test; WRAML = Wide Range Assessment of Memory and Learning; Beery = Beery Developmental Test of Visual Motor Integration.

were met. The Conners' Parent and Teacher Rating Scale Revised revealed impairment in realms consistent with ADHD.

Psychoeducational assessment scores are summarized in Table 1. Performance ranged from average to above average in all areas of intelligence and academic achievement. Nonetheless, a significant discrepancy (28 point) between his Perceptual Reasoning and Verbal Comprehension score was observed.

These case reports are suggestive of a link between NF-1, cognitive impairment, and ADHD symptoms. Case 1's cognitive and learning difficulties are characteristic of the mild but pervasive impairment that has been reported in the literature. In contrast, the discrepancy between perceptual and verbal reasoning abilities demonstrated in Case 2, in the context of average to above average intelligence, highlights the variability of cognitive findings in NF-1.

Despite longstanding anecdotal evidence that attention difficulties, hyperactivity, and impulsivity are frequently reported in children with NF-1, this area grew to be the focus of investigation only in the last decade. Studies using continuous performance tests (CPT), have offered mixed results. One study reported that children with NF-1 and comorbid ADHD experience more errors of commission compared to children with NF-1 alone, children with ADHD alone, and unaffected sibling controls (Mautner et al., 2002). In contrast, Mazzocco

et al. (1995) found that children with NF-1 demonstrated significantly more errors of omission than their siblings, but did not differ in commission errors or overall response times. Dilts et al. (1996) found no differences between NF-1 affected children and unaffected siblings on a CPT. Moreover, Moore et al. (1996) found no difference between children with NF-1 and the normal population on the Trailmaking Test and the Freedom from Distractibility Deviation Quotient, measures thought to be reflective of ADHD symptomatology. To summarize, neuropsychological measures of attention expose some link between attentional deficits and NF-1; however, the small sample sizes, limited number of studies, and lack of uniform findings, indicate that the strength of the association is unclear.

Studies using self-report measures or clinician rated interviews provide stronger evidence to support an association between attentional difficulties, ADHD, and NF-1. Parents report more ADHD related behaviours in children with NF-1 compared to their sibling controls (Schrimsher et al., 2003). In a separate study, 46 out of 93 NF-1 affected children consecutively referred to an outpatient NF-1 clinic met DSM IV criteria for ADHD (Mautner et al., 2002). Moreover, in a series of 36 children with NF-1 referred for MRI, none of whom had been specifically referred for inattention or other cognitive problems, one third of the sample were identi-

fied as having ADHD (Kayl et al., 2000).

Diagnostic imaging studies have suggested an association between the presence of Unidentified Bright Object's (UBO's) in the diencephalon and poorer performance on neuropsychological measures of attention (Moore et al., 1996). UBO's are focal areas of increased signal intensity, apparent on MRI in approximately 70% of children and adolescents with NF-1, and postulated to be related to the cognitive deficits associated with the disorder (Kayl & Moore, 2000). Further evidence suggesting a link between brain pathology and attentional deficits includes the findings of Kayl et al.'s (2000) MRI study which compared 36 children with NF-1 to 18 controls and revealed that teacher and parent reports of attentional difficulties were associated with a smaller splenium and smaller total corpus collosum. Clearly, the limited number of studies and small sample sizes makes it impossible to draw conclusions about this data at this point in time.

Information regarding response to treatment is also limited. Only anecdotal evidence supporting the use of stimulant medication was available until Mautner et al.'s (2002) study of 93 children with NF-1 which reported similar efficacy for methylphenidate in the

treatment of ADHD in children with and without NF-1. More studies are needed to corroborate these findings.

With prevalence rates of ADHD in children with NF-1 estimated to be as high as 30%, and reports of attentional deficits evident throughout the literature, the paucity of studies investigating this relationship is surprising. A potentially contributing factor may be related to the lack of exploration of this area in the psychiatric literature. To date, all relevant studies having been published in journals of pediatrics, neurology, and psychology. Future collaboration between NF-1 experts and Psychiatry may lead to increased opportunities for research and an enhanced understanding of the psychopathology associated with NF-1. Review of these cases highlights the importance of completing a comprehensive neuropsychological evaluation of children with NF-1 to assess for cognitive and learning impairments as well as psychopathology. Psychiatrists should also add NF-1 to the list of genetic conditions that they consider when learning and/or attentional deficits are identified, as it is possible that some individuals may come to the attention of psychiatrists prior to receiving an NF-1 diagnosis. Finally, clinicians should be familiar with the limitations of

Commentary

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This case description and discussion highlights the importance of Neurofibromatosis type 1 (NF-1) to child psychiatrists. NF-1 is a common genetic condition, with frequent complications related to learning, cognition, attention, social skills, and features of autism spectrum. Several other issues may be important to the child psychiatrist and warrant discussion. The common skin manifestations of NF-1, including café au lait macules and neurofibromas, and the less common but more complicated physical features, such as large plexiform neurofibromas and scoliosis, have an important impact on self esteem of children and adolescents with NF-1. Some children develop lesions of the central nervous system, including optic pathway gliomas or other low grade tumors which may further complicate their cognitive and social development. The unpredictable and progres-

sive nature of NF-1, and the paucity of effective interventions contribute to child and parent anxiety, depression and sense of helplessness. Half of children with NF-1 have a parent with NF-1, who may also experience physical, learning and mental health complications, and possibly feelings of guilt. Parents often feel overwhelmed by the challenges of mastering the education system and accessing experts in mental health. Finally, the psychiatrist may play a role in identifying children with NF-1, which often goes unrecognized.

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the current literature in this area and be aware of the need for further research, particularly with respect to treatment implications.

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