

## Cognitive functions in neurofibromatosis type 1 patients and unaffected siblings

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Attention, learning, and perceptual problems have been reported at various degrees and rates in neurofibromatosis type 1 (NF1). We aimed to define the cognitive profiles frequently associated with NF1. Children and adolescents with NF1 (n=58) were tested using Wechsler Intelligence Scales for Children-Revised (WISC-R), Judgment of Line Orientation, and Bender Visual-Motor Gestalt tests. Comparison groups were unaffected siblings of NF1 patients (n=20), children with attention deficit and hyperactivity disorder (ADHD, n=40), and normal children (n=40). No difference was found between familial or sporadic NF1 cases. Seventeen/58 (29%) of NF1 cases had a full scale IQ <70. The subgroup of NF1 patients with full scale IQ >80 (n=27) scored lower in WISC-R subtests measuring visual perception when compared to a healthy control group of similar intelligence, and lower in arithmetic but better in Bender-Gestalt and Judgment of Line Orientation tests when compared to an ADHD group of similar intelligence. These results indicate a high prevalence of mental retardation in a clinical NF1 series. NF1 patients who have normal intelligence may have impaired visual perception, but their visual perceptual problems are less than in ADHD. The tendency of unaffected siblings of NF1 patients to have mildly but consistently low test scores compared to healthy controls needs to be studied further for underlying genetic or environmental factors.

**Key words:** neurofibromatosis type 1, NF1, cognitive, learning, mental.

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder with a prevalence of 1 in 3,000-4,000. Forty-80% of children with NF1 have some form of cognitive or behavioral impairment<sup>1,2</sup>. Mental retardation, defined as full scale intelligence quotient (FSIQ) <70, is only slightly higher in children with NF1 than in the general population, but discrepancies between Verbal IQ (VIQ) and Performance IQ (PIQ) in both directions<sup>2-4</sup>, and impairment in visual-spatial functions, spatial memory, and visual-motor integration skills, as illustrated by poorer performance in Bender Visual-Motor Gestalt (BG) and Judgment of Line Orientation

(JLO) tests<sup>5,6</sup>, appear among the most common neuropsychological deficits.

Learning disabilities (LDs) have been reported in 30-60% of NF1 patients<sup>1,5</sup>. Of these, most are visual-perceptual (i.e., nonverbal) LD. Cutting et al.<sup>7</sup> compared the nature of LD in NF1 with LD in the general population. The NF1 group scored significantly lower than the "developmental LD" group on visual-spatial measures, suggesting more severe impairment. Up to 40% of children with NF1 also have problems with attention or impulse control, meeting the diagnostic criteria of attention deficit-hyperactivity disorder

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(ADHD)<sup>3</sup>. Attention problems may affect school performance in NF1: children with NF1 who have at least one ADHD feature were more likely to repeat grades at school<sup>8</sup>.

Comparison between studies is limited by differences in study design, in definitions for terms like “specific learning disability”, and because of population biases caused by inclusion of patients with intracranial pathology, recruitment of patients from LD clinics, or the choice of control groups. Most studies investigated cognition in mixed groups of familial and sporadic NF1 cases, using their unaffected siblings as the control group. Although the somatic phenotype and genetic mutations described in familial and sporadic NF1 are similar, the number of affected family members might influence the cognitive profile. In this study, we intended to examine cognition in children with familial and sporadic NF1 through a multivariate combination of three neuropsychological tests: Wechsler Intelligence Scales for Children-Revised (WISC-R), Bender Visual-Motor Gestalt (BG), and the Judgment of Line Orientation (JLO), and to make comparisons with unaffected siblings, children with ADHD, and normal children.

## Material and Methods

### Participants (Table I)

A total of 158 children were included in this study: children with NF1 and a parent with

the disease (NF1-familial, n=29), children with NF1 and no other affected family members (NF1-sporadic, n=29), unaffected siblings of children with NF1 (NF1-sib, n=20), children with ADHD (n=40), and children with no neurological problems (control, n=40). The diagnosis of NF1 was made according to the criteria of the National Institutes of Health<sup>9</sup>. Children with central nervous system or other systemic conditions that may affect test performance, such as epilepsy and brain tumors, were excluded. Children with stable optic glioma and no visual impairment were included. The unaffected siblings of children with NF1 were examined by a child neurologist and an ophthalmologist to rule out NF1; when there was more than one sib in the family, the sibling of closest age was included in the study.

The ADHD group consisted of newly diagnosed children according to the Diagnostic and Statistical Manual (DSM-IV)<sup>10</sup>. Neurological and systemic disorders, children on medication and those with uncorrected hearing or visual problems were excluded. In order to screen for comorbidities and support the diagnosis of ADHD, the Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL) Diagnostic Interview, a structured interview formed to detect a wide array of past and present psychopathology in children and adolescents

Table I. Characteristics of Research Groups

Patient groups	Sex	N	Age range (years)	Mean age
NF1 cases	F	15	7-23	12.4
	M	16	8-22	8.4
IQ<79	F	14	8-23	11.1
	M	13	7-15	10.5
IQ≥80	F	15	8-23	12.5
	M	14	7-15	11.1
Familial	F	14	7-20	11.9
	M	15	8-24	12.4
Sporadic	F	16	7-19	13.2
	M	4	7-14	9.5
Unaffected siblings of NF1	F	20	8-13	9.8
	M	20	7-13	10.2
ADHD	F	20	8-14	10.1
	M	20	8-13	10.2
Control	F	20	8-14	10.1
	M	20	8-13	10.2

NF: Neurofibromatosis. IQ: Intelligence quotient. ADHD: Attention deficit hyperactivity disorder.

according to DSM-III and DSM-IV criteria<sup>11,12</sup>, and Conners Parent and Teachers' Rating Scales<sup>13-16</sup>, all adapted and validated for Turkey, were applied.

The healthy control group consisted of volunteering age-matched children with no known health or learning problems from schools and well-child clinics in the same district. Patients with undiagnosed or unreported LD in the ADHD and control groups were excluded if deficits in one of these criteria were observed: discrepancy between VIQ and PIQ exceeding 15 points on the WISC-R profile, DSM-IV criteria for ADHD and LD, or a previously validated standard quiz assessing the reading, writing and mathematic skills appropriate for the child's age and grade<sup>17</sup>. Socioeconomic status was assessed as "low" or "middle and high" in all groups according to parental education and income. Signed informed consent from the parents and assent from all subjects were obtained. The study was approved by the institutional ethics committee.

### **Neuropsychological Tests**

#### **1. Wechsler Intelligence Scales for Children-Revised (WISC-R):**

This is an intelligence test for children between the ages of 6-16 that can be completed without reading or writing. It consists of two scales, the Verbal and Performance Scales, each with several subtests<sup>18</sup>. The Verbal Scale measures language expression, comprehension, listening, and the ability to apply these skills to solve problems. The examiner asks the questions orally and the child gives a spoken response. We used five verbal subtests of the WISC-R: Information, Similarities, Arithmetic, Comprehension, and Digit Span. The Performance Scale assesses nonverbal problem solving, perceptual organization, speed, and visual-motor proficiency. Included are tasks like puzzles, analysis of pictures, imitating designs with blocks, and copying. We used five performance subtests of the WISC-R: Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Coding. The VIQ and PIQ obtained from the test are the summary measures of verbal and performance skills, and the FSIQ, based on the 10 tests included in the VIQ and PIQ scales, is an index of general intellectual functioning.

The WISC-R was adapted and standardized in Turkey in 1997. A few items were changed, but in general the Turkish version closely resembles the original version. Approximately 11 age groups (6-16 years) constituted the standardization sample. Test-retest reliabilities were 0.97 for VIQ, 0.93 for PIQ, and 0.97 for FSIQ. Subtest reliabilities ranged between 0.51-0.86<sup>19</sup>.

#### **2. The Bender Visual-Motor Gestalt Test (BG):**

This is a psychological assessment used to evaluate visual-motor functioning, visual-perceptual skills, neurological and emotional disturbances, and mostly functions of the non-dominant parietal lobe, in individuals aged three and older. It is also used to evaluate visual-motor maturity and to screen children for developmental delays<sup>20</sup>. Test-retest reliabilities in the Turkish standardization ranged from 0.73- 0.97<sup>21</sup>. Impairment in the listed functions is associated with high scores.

#### **3. The Judgment of Line Orientation (JLO) Test:**

Judgment of Line Orientation (JLO) is an assessment of visual recognition and visual-spatial functioning in subjects aged three and older. It measures the functions of the non-dominant cerebral hemisphere and mostly parietal lobe<sup>22</sup>. Its standardization for Turkey was done with test-retest reliabilities of 0.85<sup>23</sup>. Impairment in the listed functions is associated with low scores.

### **Statistical Analysis**

The Statistical Package for the Social Sciences (Windows version 13) multivariate analysis of covariance (MANCOVA) was used to compare the scores of each test and subtest between groups. Specific differences were examined with Bonferroni adjustment, using a p value of <0.05 as significant. The reasons for the choice of MANCOVA were the continuous nature of our dependent variables (test scores), the number of dependent variables, multiple levels of independent variables, and the possibility to take socioeconomic status into consideration.

### **Results**

Neurofibromatosis (NF1)-familial and NF1-sporadic patients had similar scores on all tests and were combined in one single group

for further analysis. Five children with NF1 and optic glioma showed no particular deficit in tests requiring visual input, and were not excluded from the group. NF1-sibs from familial and sporadic NF1 groups did not differ in VIQ, PIQ and FSIQ ( $p=0.31$ ).

Mental deficiency: FSIQ  $<70$  was seen in 17/58 patients (29%), and FSIQ  $<79$  in 31/58 patients (53%). Only 10/58 NF1 patients had FSIQ  $>90$ , and the mean FSIQ of the NF1 group was 76.9, compared to 115.6 in control children. ANCOVA (socioeconomic status covariance variable) was used to test the difference between VIQ-PIQ. The differences were more pronounced in the NF1 than control groups ( $f: 3.70$ ;  $p: 0.014$ ). There were group differences in WISC-R subtests, VIQ, PIQ, FSIQ, BG Total Score, and JLO Total Score (Wilks  $\lambda=0.13$ ,  $p<0.0001$ ), confirmed by post-hoc Tukey test analysis, demonstrating that children with NF1 performed significantly lower than controls in all WISC-R subtests.

In order to investigate specific impairments, groups with comparable IQ scores-NF1 patients with IQ  $\geq 80$  and ADHD and control patients with IQ between 80-120 - were evaluated. Multivariate analysis of variance showed that the group variable (NF1, NF1-sibling, ADHD, control) was significant (Wilks  $\lambda=0.00$ ,  $p<0.000$ ). There were group differences in Arithmetic, Digit Span, Picture Completion, Block Design, Object Assembly, VIQ, PIQ, FSIQ, BG Total Score, and JLO Total Score. Post-hoc analysis (Bonferroni adjusted) demonstrated that children with NF1 performed significantly lower than controls in Arithmetic, Picture Completion, Block Design, and Object Assembly subtests of WISC-R, as well as in VIQ, PIQ, FSIQ, and JLO, and significantly lower than NF1-siblings in JLO. They scored better than the ADHD group in BG and JLO and lower in arithmetic (Table II). Six siblings and 8 NF1 patients in the total group and 4 siblings and 4 NF1 patients in the NF group with IQ $>80$  met the criteria of ADHD.

NF1-siblings performed significantly lower than the control children in Block Design and JLO. They scored better than ADHD in BG and JLO.

Children with ADHD performed significantly lower than the control group in Arithmetic, Digit Span, Block Design, Object Assembly, VIQ, PIQ, FSIQ, BG, and JLO.

## Discussion

Cognitive and behavioral impairment in NF1 has been related to the brain parenchymal lesions on magnetic resonance imaging (MRI), abnormal corticogenesis and abnormal myelination<sup>2</sup>. Recently, the association of well-circumscribed T2-hyperintense lesions in the thalamus with cognitive impairment drew attention to the location of the parenchymal lesions<sup>24</sup>. Possible molecular mechanisms involving the functions of the neurofibromin protein may include increased Ras activity, increased GABA-mediated inhibition, or impaired vesicle trafficking<sup>25,26</sup>. However, a definite link between the genetic and cognitive mechanisms is lacking.

Children with NF1 had lower scores on many cognitive and visual perceptual tests compared to the control groups in our study. Mental retardation has been reported between 6-11% in the literature<sup>2,27</sup>. The higher figures in our study (29% with FSIQ  $<70$ ) may reflect the profile of a hospital population referred to a child neurology department at the tertiary-care level, or because previous studies classified most such children as LD<sup>3</sup>. The pattern of impairment did not show any particular feature: all subtest scores were lower than in control children, and no trend was observed for verbal or performance IQ being more affected. However, visual perceptual deficits were common: nearly all children with NF1, including those with normal FSIQ, had impairment in at least one visual test (visual perception, visual motor, visual memory). This is in agreement with impaired spatial memory and visual-spatial functioning observed in most studies, although certain series reported intact visual memory and selective attention<sup>1-3</sup>. Spared and impaired functions both in verbal and nonverbal domains of WISC-R have been reported: Picture Completion and Picture Arrangement were spared, while Vocabulary and Block Design subtests were impaired<sup>28</sup>.

Because the general intelligence level would affect comparisons between test results and groups, we controlled for IQ by analyzing NF1 patients with normal FSIQ separately. Even with a FSIQ  $>80$ , NF1 children had lower scores than control children in Picture Completion, Block Design and Object Assembly, subtests related to spatial perception and organization.



Table II. Test and Sub-Test Results of Groups Matched for Total IQ\*

Variable	NFI		NFI-Sib		ADHD		Control		F	Comparison
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD				
Information	8.52 ± 2.65	9.25 ± 2.54	8.82 ± 2.13	10.07 ± 1.84	2.47					
Similarities	10.56 ± 2.53	9.87 ± 3.52	10.97 ± 2.53	11.71 ± 1.65	0.71	NF<ADHD (p=0.0412) ADHD<Control (p<0.0001)				
Arithmetic	8.76 ± 2.76	10.19 ± 2.23	8.85 ± 2.32	11.75 ± 1.92	9.47					
Comprehension	9.00 ± 1.73	9.87 ± 1.89	10.58 ± 2.25	10.68 ± 2.14	1.02	ADHD<Control (p=0.0019)				
Digit Span	8.4 ± 2.31	8.87 ± 2.42	8.79 ± 2.23	10.89 ± 1.95	5.04					
Picture Completion	9.16 ± 2.19	9.87 ± 2.50	10.64 ± 2.29	11.96 ± 1.86	4.02	NF<Control (p=0.0009)				
Picture Arrangement	8.48 ± 2.63	9.87 ± 3.42	9.45 ± 2.75	10.86 ± 2.61	2.42	p=ns				
Block Design	8.36 ± 2.60	9.31 ± 2.52	9.36 ± 2.90	12.18 ± 2.47	9.37	NF<Control (p=.0001) NF-Sib<Control (p=0.0087) ADHD<Control (p=0.0004)				
Object Assembly	9.00 ± 2.75	9.94 ± 2.41	9.97 ± 2.90	12.79 ± 1.75	7.57	NF<Control (p=0.020) ADHD<Control (p=0.0001)				
Coding	9.32 ± 2.88	9.75 ± 2.41	9.82 ± 2.97	10.86 ± 1.43	1.06					
VIQ	93.76 ± 11.6	97.81 ± 10.90	98.06 ± 9.85	107.00 ± 8.28	5.06	NF<Control (p=0.0001) ADHD<Control (p=0.0037)				
PIQ	92.04 ± 13.3	98.25 ± 12.70	98.85 ± 11.20	113.50 ± 9.72	10.97	NF<Control (p=0.0001) ADHD<Control (p=0.0001)				
TIQ	92.24 ± 12.4	98.00 ± 9.84	98.09 ± 9.87	110.50 ± 8.12	10.11	NF<Control (p=0.0001) ADHD<Control (p=0.0001)				
BG Total Score	4.4 ± 3.15	3.87 ± 4.06	7.18 ± 3.3	2.68 ± 1.66	11.27	NF<ADHD (p=0.050) NF-Sib<ADHD (p=0.050) ADHD>Control (p=0.0001)				
JLO Total Score	11.44 ± 3.24	15.69 ± 4.61	8.54 ± 2.29	18.25 ± 3.04	52.34	NF<Control (p=0.0001) NF<NF-Sib (p=0.0005) ADHD<NF-Sib (p=0.0001) ADHD<Control (p=0.0001) ADHD<NF (p=0.050)				

\* Only NFI patients with total IQ>80 were included.

NF: Neurofibromatosis. ADHD: Attention deficit hyperactivity disorder. VIQ: Verbal intelligence quotient. PIQ: Performance intelligence quotient. TIQ: Total intelligence quotient. BG: Bender Visual-Motor Gestalt. JLO: Judgment of Line Orientation.

Hyman et al.<sup>2</sup> noted that many significant differences between NF1 and unaffected sibling controls disappeared when IQ was controlled for, but differences between NF1 and siblings persisted in the JLO and spatial relations tasks. The only domains in which deficits were greater than predicted by IQ were reading, spelling, planning, perception (visuospatial and visuo-perceptual), and sustained attention. Our results also indicate that NF1 patients with normal IQ differ from controls in processing visual information. It appears important to control for IQ when diagnosing specific deficits in NF1, especially in hospital populations.

Neurofibromatosis-1 children scored lower than the ADHD group only in Arithmetic, and, as expected, better than ADHD in BG and JLO. Attention problems have often been reported in children with NF<sup>3,8</sup>: in our series, attention did not present as a frequent problem when IQ was controlled for. Although some children in the NF1 and NF-sib groups met the criteria for ADHD and the NF1 and ADHD groups scored similar in visual-spatial subtests, which have a clear relationship with attention, the ADHD group manifested more pronounced impairment in BG and JLO.

In contrast with most studies using siblings as the only control group, we compared NF-sibs to other control groups. There was no difference between NF1 with normal IQ and NF1-sibs except on the Block Design subtest. Interestingly, siblings of NF1 patients performed lower than healthy control children in almost all tests: although the differences were not significant, scores of the NF-sib group were consistently between NF1 and control values. Because our analyses were corrected for socioeconomic status and NF1 had been ruled out in these children through a detailed clinical evaluation done after 6 years of age (when the cutaneous stigmata of NF1 would be apparent), we can speculate on certain other mechanisms for this finding: biological causes involving genetic characteristics in the proximity of the NF1 gene, or environmental causes, i.e., the effect of a sibling with NF1 and visual-perceptual problems, may be implicated. Children with NF1 have deficiencies in emotional adjustment and quality of life<sup>29</sup>. It is possible that NF1 patients being followed-up in a hospital setting have more severe psychological impairment, rendering their siblings more susceptible

to cognitive and attention problems. In any case, this finding questions the validity of control groups consisting of siblings of NF1 patients used in various reports. More detailed studies including siblings from various ages, or comparisons between siblings according to birth order, might bring further information. Our results point to the degree and frequency of cognitive impairment in NF1 even in the presence of normal IQ and to the need for comprehensive assessment including family and home environments.

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