

ORIGINAL ARTICLES

Patterns of cognitive functioning in school-aged children with Noonan syndrome associated with variability in phenotypic expression

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Objective: To evaluate the cognitive profiles of children with Noonan syndrome (NS) and to relate these profiles to measures of overall clinical severity.

Study design: Thirty-five children with NS between the ages of 7 and 18 years were tested on their intellectual, psychosocial, and academic functioning. The diagnosis of NS was established on the presence of a typical face, the characteristic heart defect, thorax deformity, short stature, affected first-degree relative(s), and cryptorchidism in male subjects.

Results: The total group of children with NS ($n = 35$) achieved significantly lower mean full-scale IQ, verbal IQ (VIQ), and performance IQ (PIQ) scores (between 85.9 and 89.3) than expected

based on normative data. The individual full-scale IQ scores varied between 48 and 130. Because of this wide range of individual scores, the mean group values are not extremely informative. The mean full-scale IQ for the group with moderate NS (n = 19) is 90.8; for the children with severe NS (n = 16) the mean full-scale IQ is 80.6. The patterns of discrepancies between VIQ and PIQ are: (1) an extreme discrepancy between VIQ and PIQ is most likely to emerge in children with severe NS with (low) average intellectual abilities; (2) children with moderate NS are more likely to attain similarities in VIQ and PIQ scores; and (3) children with moderate NS demonstrate a particular pattern of discrepancy between VIQ and PIQ (ie, VIQ > PIQ).

Conclusion: For children with NS, the findings on physical examination are indicative of the pattern of cognitive abilities. NS is not associated with substantial deficits in the level of intellectual functioning or with a single/unitary cognitive pattern. Severe NS expression, however, predicts in part a specific pattern of deficits and capacities in cognitive functioning. (J Pediatr 1999;135:707-13)

CBCL

Child Behavior Checklist

NS

Noonan syndrome

PIQ

Performance IQ

RPM

Raven Progressive Matrices

VIQ

Verbal IQ

VMI

Visual-Motor Integration

See related articles, p. 667 and p. 703.

Noonan syndrome is a well-known autosomal dominant condition characterized by a typical face, short stature, and a congenital heart disease. Mild mental retardation has been described as a feature of the syndrome.^[1] The incidence of NS has been estimated as 1 in 2000 live births,^[2] which makes NS one of the more frequently occurring multiple congenital anomalies syndromes. In the absence of a specific biochemical marker, the diagnosis of NS is still based on clinical criteria. A gene for autosomal dominant NS has been found on chromosome 12q, but this gene has not been characterized yet.^{[3] [4]}

The phenotypic expression of NS is highly variable and changes with age.^[5] In childhood the typical face has a triangular shape with a high broad forehead and a pointed chin, hypertelorism, ptosis, downward-slanting palpebral fissures, low-set posteriorly rotated ears with a thick helix, and a short broad neck with a low hairline. The most common heart defects are pulmonary valve stenosis in 65% of the patients and/or a hypertrophic obstructive

cardiomyopathy in 20%. Other features frequently seen in NS are pectus deformities (up to 95%) and cryptorchidism in male patients (77%).

Most review articles mention mild mental retardation in 15% to 35% of patients with NS.^{[2] [6] [8]} However, there are only limited data on cognition and intelligence in NS. Money and Kalus^[9] described IQ and specific disabilities in 8 male patients. They reported full-scale IQ scores that were variable, ranging from 64 to 127. One patient showed substantial verbal disabilities, and 4 patients had major apractic disabilities. The authors comment that despite the small number of patients, their study indicated that involvement of cognition in NS is sporadic.^[9] In 1988 Finegan and Hughes^[10] reported one affected member of a family with NS who had very superior intelligence (full-scale IQ of 133). Comish^[11] reported strengths in non-verbal skills and weakness in verbal skills in a mother and 2 daughters with NS. Recently, a study of cognitive abilities in 51 children with NS with a mean age of 9 years 7 months demonstrated a mean (SD) full-scale IQ of 84.3 (21.6), and in 41% of the cases the verbal IQ was lower than the performance IQ (M. Patton, unpublished data).

The primary aim of this study was to evaluate the cognitive profiles of children with NS. Because we hypothesized that the intellectual phenotype could be related to the clinical phenotype of NS, we established indices for general levels of intelligence (IQs) and cognitive profiles (VIQ and PIQ) for 35 school-aged children with NS and related these indices to 2 subtypes of phenotypic expression in NS.

SUBJECTS AND METHODS

Clinical Diagnosis

Thirty-five children with NS between the ages of 7 and 18 years were tested on their intellectual, psychosocial, and academic functioning. The diagnosis of NS was established based on the presence of a typical face, the characteristic heart defect, typical thorax deformity, short stature, affected first-degree relative(s), and cryptorchidism in male subjects. Children with a typical face had to have at least one other major characteristic of the syndrome, whereas those with suggestive facial findings had to have at least 2 other major characteristics in order to be diagnosed as having NS.^[2]

Relevant clinical information about the children was obtained from their hospital case notes, parental accounts, and clinical examination. This included features diagnostically relevant for NS such as weight and height curves, major feeding problems in infancy, hypotonia, recurrent otitis, ocular abnormalities, and a history of easy bruising. Twenty-nine of the 35 children with NS were also evaluated on their socio-emotional functioning by the Child Behavior Checklist, completed by a primary caretaker (mothers, 82%; fathers, 11%; other, 7%) after informed consent was obtained.

Phenotypic Patterns of NS

For subject classification of NS expression, 4 major physical characteristics of NS were applied: (1) facial findings, (2) cardiac defects, (3) short stature, and (4) chest wall deformities. According to the nature of these 4 characteristics, we made a subdivision between major (A) and minor (B) characteristics. These major versus minor features are (1) typical face versus suggestive face, (2) pulmonary valve stenosis and/or hypertrophic obstructive cardiomyopathy versus other congenital heart defects, (3) height below the 3rd percentile versus height below the 10th percentile, and (4) pectus carinatum/excavatum versus broad thorax with large inter-nipple distance. Based on the pattern of these phenotypic characteristics, each patient received a severity rating of NS expression.

Intellectual Assessment

The Dutch adaptation of the Wechsler Intelligence Scale for Children-Revised^[12] was used to assess intellectual ability. The full-scale intelligence (total IQ) of the WISC-RN is based on 12 subtests, each designed to measure either the verbal or performance ability of a child. In the verbal section the tests are Information, Similarities, Arithmetic, Vocabulary, Comprehension, and Digit Span. In the performance section the tests are Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding, and Mazes. Each section is scored separately, and both a "verbal IQ" and a "performance IQ" are obtained. The mean value of the total, verbal, and performance IQ scores is 100 (SD = 15). A substantial difference between VIQ and PIQ of more than 11 points is considered clinically important for a disparity in cognitive pattern.^[13] An IQ range between 51 and 70 was typified as "mildly mental retarded" (*International Classification of Diseases, Ninth Revision, Clinical Modification*) according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* classification. Several areas of cognitive functioning (eg, verbal comprehension, perceptual organization, spatial knowledge, sequencing abilities, memory, freedom from distractibility) were evaluated by regroupings of WISC subtests proposed by Bannatyne^[14] and Kaufman.^[15] In addition to the WISC-RN, the Visual-Motor Integration (VMI) and Raven Progressive Matrices cognitive tests were used to evaluate perceptual and motor skills^[16] and inductive reasoning ability.^[17] The youngest children (<9 years) received the colored version of the Raven test, whereas for the older children the standard (uncolored) version was used. For 2 subjects (17 and 18 years old), an adult version of the WISC-RN (the Wechsler Adult Intelligence Scale) was used. The WISC-RN subscale Mazes was added, because the WAIS does not include this subtest. Lezak^[18] indicated that it is appropriate to use the Mazes subscale and its highest WISC-R norm (16.0-16.5) to estimate the adequacy of the adult performance.

Statistical Analyses

In order to facilitate comparison among the WISC-RN test and the 2 other cognitive tests (ie, VMI and RPM), the percentile scores of the latter tests were converted to age-related IQ equivalents. Means and SDs were computed for all IQ-related measures of the WISC-RN, RPM, and VMI. For a comparison of means, standard parametric methods of analysis were used when scale properties permitted this. Two-tailed *t* tests were used to compare the means of the different subtests and subscales of the WISC-RN, and a 1-tailed paired *t* test was used to assess directional differences. To investigate linear relationships between clinical and intellectual data, Spearman R coefficients of correlation were computed for those variables measured on an ordinal scale.

Statistical evidence was found at *P* levels of .05. All data were entered and analyzed by using SPSS/PC (SPSS-WIN, 1993). Test administration and analysis were carried out by the same examiner (G.T.) for all 35 cases.

RESULTS

Clinical Data

The sample consists of 23 boys and 12 girls.*

*Individual subject data are available from the authors on request.

Besides the 22 patients with a typical heart defect, 2 patients had a coarctation of the aorta and one had an atrial septal defect with mitral valve insufficiency. In 10 patients (29%) no congenital heart disease was present. At the time of diagnosis, height was below the 3rd percentile in 26

children (74%); at the moment of cognitive testing, 20 of these (57%) still had a height below the 3rd percentile. Of the total sample of 35 children with NS, 19 children (54%) received growth hormone therapy. The mean duration of treatment at the time of the intellectual assessment was 2 years. The remaining 6 children had reached a height just above the 3rd percentile at the moment of cognitive testing. Seventeen (74%) of the 23 boys had undescended testes at birth. A history of easy bruising or bleeding was mentioned in 16 patients (46%). Major feeding problems, leading to poor weight gain in infancy, were reported in 17 of the cases (49%). Ocular abnormalities with impaired vision were observed in 15 children (43%), and recurrent otitis in 8 (23%). Two children had a drain because of hydrocephalus.

The results of the CBCL were compared with those of Dutch standard populations. The children with NS showed more behavior problems than the control group but not in the clinical area. Clusters of behavior problems that scored high in the parental reports were social problems, attention problems, and somatic complaints. No correlation was found between the total results of the CBCL and gender, age, phenotypic expression, or educational setting (Roosenboom et al, unpublished data). None of the children had the clinical diagnosis of attention-deficit/hyperactivity disorder.

Sample Characterization According to Phenotypic Expression

The distribution of males and females in the sample was approximately 2:1 (Table I).

Table I. Classification by sex, age, and education at date of intellectual assessment

Phenotypic classification	Total No.	Sex		Age group		Education type	
		Male	Female	6-12 y	12-18 y	Regular	Special
Severe NS	16	11	5	9	7	5	11
Moderate NS	19	12	7	6	13	15	4
Total	35	23 (66%)	12 (34%)	15 (43%)	20 (57%)	20 (57%)	15 (43%)

Similar gender rates were observed for both phenotypic subgroups. The over representation of males in this study proved not statistically significant ($\chi^2 = 3.46$, $df = 1$, $P = .063$). The mean age of the children at intellectual assessment was 12.4 years (range, 7.4-18.1 years). Fifteen children (43%) required special education at schools for children with severe learning disorders, which is significantly greater than the 4% of the Dutch school-aged population that attend these schools ($\chi^2 = 41.98$, $df = 1$, $P < .001$).

Of the children with the classification "severe NS," almost 70% (11/16) attended schools for children with severe learning disorders, compared with 21% (4/19) of the children with "moderate NS."

General Level of Intellectual Ability

As a group, the children with NS achieved significantly lower mean full-scale IQ scores than expected based on normative data (mean = 100, SD = 15) ($t = -3.24$, $df = 68$, $P < .05$) (Table II).

Table II. IQ scores and IQ equivalents for patients with NS

IQ scores	Total population			Severe NS			Moderate NS		
	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.
Full-	86.14	20.39	35	80.63	20.39	16	90.79	19.24	19

scale IQ									
VIQ	89.26	19.28	35	82.13	19.75	16	95.26	17.14	19
PIQ	85.86	21.25	35	84.06	23.29	16	87.37	19.89	19
Raven IQ	99.66	18.19	35	91.94	18.67	16	106.16	15.39	19
VMI IQ	90.94	14.39	35	88.13	15.72	16	93.32	13.12	19

Normative IQ scores: mean = 100; SD = 15.

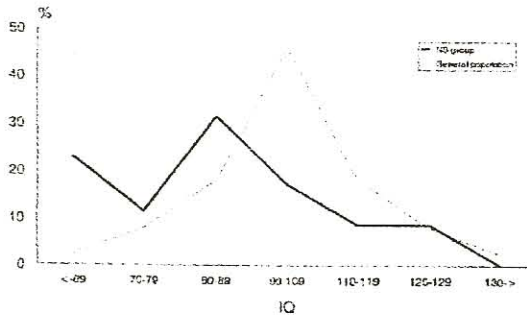
In 34% of the children with NS, we observed average intellectual abilities (IQs 85-115). This proportion is significantly smaller than the 68.2% in the general population ($\chi^2 = 12.94$, $df = 1$, $P < .001$). Mental retardation (IQ below 70) was present in 8 children (23%), which is significantly greater than in the general population (2.3%) ($\chi^2 = 65.82$, $df = 1$, $P < .001$). The proportion of children performing in the range of borderline or superior intelligence was as expected under a normal distribution ($\chi^2 < 3$).

The mean scores for full-scale IQ, VIQ, and PIQ were quite similar (between 85.9 and 89.3). These IQ scores represent "low-average" intellectual capabilities. The measures of the Raven IQ and the VMI IQ point out that the children with NS, as a group, had adequate (average) inductive reasoning and visual-motor abilities.

The intra-group variability, defined as the coefficient of variation (SD/mean), was high for all the IQ measures and for both subgroups of phenotypic expression. Significant differences between the 2 subgroups were observed only for VIQ and Raven IQ ($t = 2.10$, $df = 33$, $P < .05$). On these IQ measures, children with moderate NS achieved average scores in comparison with age-related standardization subject samples, whereas children with severe NS achieved below-average scores. The observed differences between both subgroups on the other IQ parameters (ie, full-scale IQ, PIQ, and VMI IQ) did not reach levels of significance ($P < .05$).

Distribution of Intelligence

A substantial number of the children with NS functioned intellectually in a borderline range (IQ <



85) (Fig 1).
 Fig. 1. Distribution of full-scale IQ for children with NS (n = 35).

This finding suggests that NS is linked with a general shift of the IQ distribution downward. Moreover, this observation led us to question whether this lowering of full-scale IQ is attributable to the effect of a specific pattern in verbal-performance discrepancy or to specific dips in performance on particular subtests.

Patterns of Discrepancy Between VIQ and PIQ

The mean difference in IQ points between VIQ and PIQ was +3.4 (15.5) in the total NS group, -1.9 (18.2) in the severe NS group, and 7.9 (11.5) in the moderate NS group (Table III).

Table III. VIQ-PIQ discrepancy (intellectual patterns) for all patients with NS

Classification	VIQ-PIQ discrepancy			
	>11 points			11 points
	VIQ > PIQ	PIQ > VIQ	Total	PIQ ~ VIQ
Severe NS	3	4	7 (44%)	9 (56%)
Moderate NS	6	0	6 (32%)	13 (68%)
Total	9 (69%)	4 (31%)	13 (37%)	22 (63%)

VIQ > PIQ: VIQ exceeds PIQ; PIQ > VIQ: PIQ exceeds VIQ.

The observed difference between VIQ and PIQ (95.3 vs 87.4) in subjects with moderate NS was not statistically significant ($t = 1.31$, $df = 36$, $P = .20$). Focusing on the direction of the discrepancies (VIQ > PIQ or PIQ > VIQ), the pattern VIQ > PIQ occurred more often than PIQ > VIQ: 9 children had a VIQ > PIQ disparity of 12 points or greater, whereas only 4 children had a PIQ > VIQ of this magnitude.

The individual performances on the VIQ and PIQ tests are displayed in an XY plot (Fig 2).

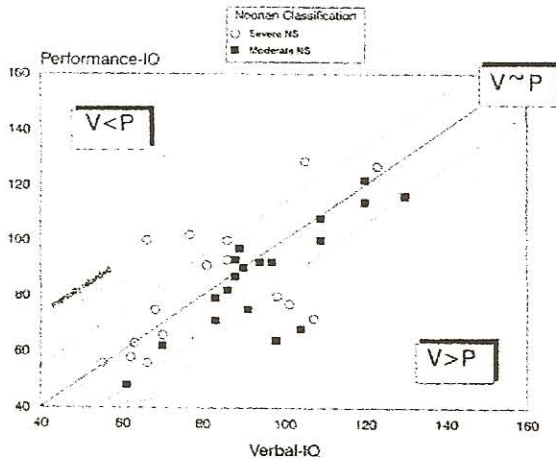


Fig. 2. Patterns of discrepancy between VIQ and PIQ for children with severe NS ($n = 16$) and moderate NS ($n = 19$), based on clinical classification for 35 cases of NS.

In order to substantiate the observed trends in patterns of VIQ and PIQ across phenotypic subgroups, separate correlations were performed. In the total population, no significant association between clinical phenotype and VIQ-PIQ pattern was found ($\tau = 0.13$, $n = 35$, $P > .10$). Because it is highly unlikely to find significant disparities between domains of intellectual functioning of mentally retarded children (because of floor effects), we excluded these subjects

from the analyses. A significant association was found between clinical and intellectual phenotype ($\tau = 0.39$, $n = 27$, $P < .05$).

Subtest Scatter

The subtest scores on the WISC-RN in the NS subgroups are presented in Table IV.

Table IV. Subtest scatter for patients with NS

Subtest	Total population		Severe NS		Moderate NS	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Verbal scale						
Information	8.3	(3.6)	6.7	(4.0)	9.7	(2.6)
Similarities	8.9	(3.7)	7.9	(3.5)	9.7	(3.7)
Arithmetic	7.9	(3.2)	6.5	(2.9)	9.1	(2.9)
Vocabulary	7.9	(3.2)	6.8	(3.9)	8.8	(4.0)
Comprehension	9.5	(3.7)	8.7	(3.5)	10.3	(3.7)
Digit Span	7.6	(3.0)	6.4	(2.8)	8.5	(2.8)
Performance scale						
Picture Completion	8.0	(3.4)	7.4	(2.9)	8.6	(3.7)
Picture Arrangement	7.7	(3.6)	6.9	(4.4)	8.3	(2.8)
Block Design	7.8	(3.7)	7.4	(3.7)	8.2	(3.7)
Object Assembly	7.5	(4.7)	7.3	(5.4)	7.7	(4.1)
Coding	8.2	(3.5)	7.1	(3.7)	9.2	(3.2)
Mazes	7.6	(4.0)	8.1	(4.4)	7.2	(3.7)
Normative subtest scores: mean = 10; SD = 1.5.						

When both subgroups were compared, the severe NS group had significantly lower mean subtest scores on acquired knowledge (subtest Information) ($t = -2.69$, $df = 33$, $P = .011$), computational abilities (subtest Arithmetic) ($t = -2.57$, $df = 33$, $P = .015$), and auditory short-term memory (subtest Digit Span) ($t = -2.19$, $df = 32$, $P = .036$).

Regroupings of the subtest scores (Table IV) revealed that particular areas of cognitive functioning are vulnerable in children with NS, namely, the ability to organize perceptual information, planning abilities, the ability to work synthetically, and spatial knowledge. The NS group performed relatively well on tasks that require verbal comprehension, abstract reasoning, and social awareness or judgment. The performance of children with severe NS was significantly poorer ($P < .05$) than that of children with moderate NS on tasks that reflect focusing attention, acquired knowledge, short-term memory (especially repetitive memory skills), and achieving without time pressure.

DISCUSSION

Based on well-standardized tests of mental ability, our results show that children with NS have a wide range in level of intelligence (IQ scores between 48 and 130). For the total NS population, the mean full-scale IQ of 86.1 is nearly 1 SD below the general population mean (IQ 85-115). Similar discrepancies are observed for the mean VIQ (89.3) and the PIQ (85.9).

Because of the wide range of individual IQ scores, the mean group values are not extremely informative. We hypothesized that there would be an association between the severity of physical expression of NS in terms of moderate and severe (clinical phenotype) and the cognitive abilities in terms of IQs (intellectual phenotype). Sixteen of the 35 children with NS (46%) participating in this study are severely affected with regard to the physical signs of NS (ie, typical facies, congenital heart defect, thorax deformity, and short stature). The other 19 children are moderately affected. When the sample is subdivided into these 2 groups, the full-scale IQ measures differ in favor of the group with moderate NS. For VIQ and on the Raven IQ test, the differences are significant. Discrepancies between VIQ and PIQ are observed in 44% of the children with severe NS and in 32% of the children with moderate NS. Extreme discrepancies between VIQ and PIQ are more prominent in children with severe NS, whereas children with moderate NS are more likely to demonstrate a particular pattern of discrepancy between VIQ and PIQ (ie, VIQ > PIQ).

The relative strengths of children with NS are non-verbal reasoning, verbal comprehension, social judgment, and visual-motor abilities. Children with NS exhibit specific weaknesses in spatial knowledge and planning abilities. This leads to limited abilities in organizing academic tasks (especially working synthetically), which leads to difficulties in school. Areas of cognitive functioning that require special attention in early school years are the child's capacities for organization, memorization, and focusing attention.

Based on the results of this study, 2 questions related to the occurrence of mental disabilities in NS and its role in school reference can be answered.

The first question is whether mental deficiency is a specific feature of NS. There is a higher prevalence of children with NS in the schools for children with severe learning disorders (43%) than in the general Dutch population (4.8%). This is especially true for children with severe NS (69% vs 21% for those with moderate NS). This finding suggests that mild mental deficiency is more frequently found in patients with NS than in healthy children, although patients with NS may have even superior intelligence.

The second question is whether the intellectual capabilities of children with NS are used as major criteria for access to special education services. First, the majority (77.7%) of children with NS and normal mental capacities (IQ > 84) attend regular schools. Two children with normal intelligence scores (89 and 93) attended schools for children with learning disorders because they had difficulty in the large classes in regular schools. The third child, who had an IQ score of 118, attended special education school at the request of his parents. Second, a 1-way analysis of variance revealed that the mean score of total IQ for children in special education is significantly lower than that for children in normal education settings ($F = 14.46$, $df = 33$, $P < .01$). These findings suggest that children with NS are referred to special schools because of below-average intellectual capacities. There was also no overrepresentation of children with NS and social and/or attention problems at the schools for severe learning disorders. However, the children with NS who attended special education schools had more somatic complaints than the children who attended regular schools (Roosenboom et al, unpublished data). For children with the diagnosis of NS, we recommend a thorough physical examination with emphasis on tests for vision and hearing. We also recommend an assessment of intellectual and academic function, as well as neuropsychologic skills, with the WISC-RN test, the VMI, and the RPM. The results of these tests point out the relative strengths and specific

weaknesses of the child with NS. The children should be tested in early school years so special attention can be given to the more limited capacities and the relative strengths exposed.

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