American Journal of Medical Genetics 10:37-50 (1981)

A Comprehensive Scoring System for Evaluating Noonan Syndrome

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A multidisciplinary team assessed 23 patients with various manifestations of the Noonan syndrome, including pulmonary valve stenosis (with leaflet dysplasia), "typical" facial appearance (including hypertelorism, epicanthic folds, flat nasal bridge, and apparently low-set ears), short stature, and mental retardation. Seven patients had a family history of the syndrome. A comprehensive scoring system was devised on the basis of frequency and severity of manifestations and results of invasive and noninvasive tests in these patients and those reported in the literature. The scoring system was condensed into a score card for clinical use and validated by "blind" application to patients with isolated pulmonary valve stenosis or suspected Noonan syndrome. Use of a scoring system to diagnose a syndrome for which there is no specific diagnostic test facilitates accuracy and decreases observer bias. In the case of unusual congenital disorders it is particularly valuable for a pediatrician in general practice.

Key words: Noonan syndrome, diagnostic scoring system

INTRODUCTION

In 1963 the Noonan syndrome was differentiated from the Ullrich-Turner syndrome (UTS) by Noonan and Ehmke [19]. The first case was probably described by Kobylinski in 1883, and further cases were reported in children with pulmonic valve stenosis (PS) and apparent UTS manifestations but normal chromosomes. More recently, other manifestations have been described [2–4, 11–13, 17, 19, 21, 26] including orbital hypertelorism, short stature, neck webbing, and sternal deformity, but there are no generally accepted criteria for establishing the diagnosis. We analyzed the manifestations of Noonan syndrome in 23 patients in order to establish criteria for an evaluative scoring system.

Received for publication March 15, 1980; revision received April 3, 1980.

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0148-7299/81/1001-0037$04.00

MATERIALS AND METHODS

We reviewed the records of all children who had attended the cardiology clinic at The Hospital for Sick Children in Toronto and selected for study those in whom Noonan syndrome had been suggested as a diagnosis. Twenty-five patients (or their parents), who lived within 100 miles of the hospital, agreed to return to the clinic for examination; two were excluded because chromosome analysis showed UTS mosaic chromosome abnormalities. The other 23 patients (12 boys, 11 girls) ranged in age from 8 months to 18.5 years (mean 8.4 years). Informed consent was obtained from parents for all aspects of the study.

Each patient was examined by every member of a multidisciplinary team, none of whom had access to the case records or was aware of the other observers' findings. The patient's history and physical characteristics were coded. Blood was obtained for chromosome analysis.

Posteroanterior and lateral chest roentgenograms were obtained at 183 cm (6 feet) focal film distance. The examiner looked specifically for pectus carinatum, derived the cardiothoracic ratio, and quantitated anteroposterior dimensions (Backer's vertebral index) [1].

Fifteen-lead scalar electrocardiography and Frank-lead vectorcardiography (VCG) were performed and the results analyzed in standard fashion. Age-related ECG-voltage criteria for right ventricular hypertrophy (RVH) were $RV_1 > 20$ mm, $SV_6 > 5$ mm, and R/S ratio ≥ 1.6 in patients less than 5 years old, and 0.8 in those 5 years or older. Our VCG criterion for RVH was that the sum of the maximal rightward vector of frontal and horizontal loops exceeded 1.2 mV.

M-mode echocardiography was performed with the patient supine and the right shoulder slightly elevated (about 30°); transducers (selected for each individual patient) were used with a commercially available model 101 ultrasonoscope (Hoffrel) connected to a strip chart recorder (Kent Cambridge Instrument Company). Volumes and wall thickness were measured and indices of function were determined by percentage shortening, ejection fraction, and systolic time intervals. Specific attention was directed to the interventricular septum and posterior wall of the left ventricle for evidence of asymmetric septal hypertrophy [23] or left ventricular outflow tract obstruction [14, 20].

Cardiac catheterization data and cine-angiogram were available on 18 patients in whom significant PS had been suspected clinically. Hemodynamic data were obtained using fluid-filled catheters and transducers (Statham Laboratories) and an optical recorder (model DR 8; Electronics for Medicine). Valvar gradients were derived from tracings made while the catheter was withdrawn across the valve. Shunt quantitation was determined using the Fick principle and dye dilution method.

High-speed 35-mm cine-angiography of the right and left ventricles was performed to identify pulmonary valve and left ventricular structure.

The heads and faces of 22 patients were photographed with measurement markers in place in the frontal and lateral planes. The carrying angle was measured in 16 patients (7 girls, 9 boys) according to the method described by Baughman, and our results were compared with those reported [10]. Measurements were made of the face, head, and ears [9] of the 10 Caucasian patients (7 girls and 3 boys, aged 7–19 years). These measurements (131 per patient), which incorporated 86 anthropometric methods, were used to determine facial proportions which were compared with norms developed in our hospital [L. G. Farkas, unpublished data].

Nine patients were examined by members of the Dental Department at the hospital. Acrylic impressions were made of the oral cavity and lateral cephalometric roentgenograms were taken and compared with those of age-matched normal patients.

RESULTS

History and Development

Prenatal and birth histories were unremarkable except that two children had been born prematurely (34 and 36 weeks gestation). Birth weight (mean 3.3 kg) was appropriate for gestational age in all cases. Seven patients had a family history of Noonan syndrome (2 paternally transmitted, 2 maternally transmitted, 2 with an affected sibling, and 1 with two affected siblings).

Growth retardation (height or weight < 25th centile) was significant in 17 patients. Weight and height ranged from less than the 3rd to the 75th centile, with means at the 14th and 22nd centile, respectively. The growth curve of these patients had declined symmetrically since birth. Incidence and severity of growth retardation were similar in both sexes. In most patients, increase in head circumference paralleled that of height and weight.

Ten patients were evidently mentally retarded; 3 were considered untrainable and were institutionalized, 3 were considered moderately retarded, and 4 either had a specific learning disability or attended a special school for children with learning or perceptual handicaps.

Radiologic Findings

The cardiothoracic ratio did not reflect severity of PS. Roentgenograms showed pectus excavatum in 8 patients; in 4 of these concomitant pectus carinatum was also noted. Vertebral indices of the 8 patients were in the lower part of Backer's normal range [1].

Electrocardiographs and Vectorcardiographs

The unusual QRS loop axes [25] with extreme right axis deviation and superior counterclockwise frontal QRS loop commonly seen in patients with Noonan syndrome were present in nine of our patients (Fig. 1). Right ventricular hypertrophy was present in 13 patients according to our ECG criteria and in these and seven others according to our VCG criteria.

Echocardiographs

Echocardiographs showed mild to moderate increase of thickness of the free wall of the right ventricle in 12 patients and enlargement of this ventricle in six. There was flat septal motion in one patient and dyssynchronous septoposterior wall motion of the left ventricle in two patients with right ventricular hypertension. Neither asymmetric septal hypertrophy nor obstruction of the left ventricular outflow tract was detected. Left ventricular function was normal or above average in all cases.

Pulmonary valve recordings showed poor definition of the "a" wave in all cases. Echocardiography indicated no specific abnormalities in patients whose angiograms showed valvar dysplasia.

Results of Cardiac Catheterization

Hemodynamics. PS was confirmed by the withdrawal tracings in all 18 patients who had undergone cardiac catheterization. The pressure gradient from the right ventricle to the main pulmonary artery (RV-MPA) ranged from 5–110 mm Hg and exceeded 50 mm Hg in six cases. Associated lesions were atrial septal defect (ASD) in two patients and ventricular septal defect (VSD) in one. Flow was small in left to right shunts: 1.5/1 and 1.6/1 in those who had ASD/PS and 1.8/1 in the patient with VSD/PS. No patient had left ventricular aortic gradient or evidence of left ventricular dysfunction. End-diastolic pressure was normal in all patients.

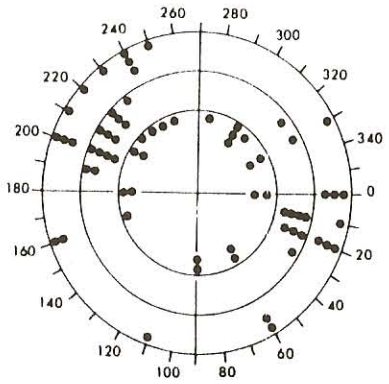


Fig. 1. QRS axis chart. Inner circle shows frontal axis according to scalar electrocardiogram (n = 22; 1 was omitted because axis was indeterminate). Middle and outer circles shown, respectively, frontal and horizontal axes according to Frank-lead vectorcardiogram (n = 23).

Results of Angiographic Studies

Right ventriculography in all 18 patients showed anterior wall thickening and coarse trabeculation in direct proportion to the RV-MPA gradient. The pulmonary valve leaflets appeared distinctly dysplastic in 12 patients, thickened in 4, and slightly thickened in 2 [16, 27]. No patient had tricuspid valve regurgitation, extensive sinusoid formation, or retrograde filling of the coronary artery. Left ventriculography showed distinct abnormalities in 12 patients – eccentric hypertrophy similar to that described by Ehlers [5, 6] and Nora [28] in four and hypercontractility in eight. (Echocardiograms of all 12 patients showed hypercontractility but were otherwise normal.) Cardiac output was normal and the left ventricular outflow tract was widely patent in all cases. Mitral valve prolapse was evident in one patient [28].

Results of Anthropometric Studies (Fig. 2)

The evaluation of the craniofacial measurements in all patients indicated vertical shortness of the face as well as horizontal and anteroposterior narrowness, which was more pronounced in the mandibular than the maxillary region. Thus, the wider than average interorbital distance appeared extraordinarily wide. The face was particularly striking in those whose interorbital distance was much greater than average, a visual impression that was accentuated in the five who had epicanthic folds.

All patients had disproportion of the nasolabial complex. The nose was shortened and widened in the root and alar regions, an appearance exaggerated by the increased length of the upper lip. The shallow nasal root and reduced protrusion of the nasal apex accentuated the width of the nose. The labial fissure was also abnormally short, particularly in the narrowest faces. This facial profile gave a visual impression of low-set ears in eight cases, but measurement by Leiber's method [8, 9] confirmed this in only four.

Facial Photographs

The posterior hairline was low in 19 patients (very low in 10 and fairly low in 9). Low posterior hairline affected the patient's appearance more significantly when associated

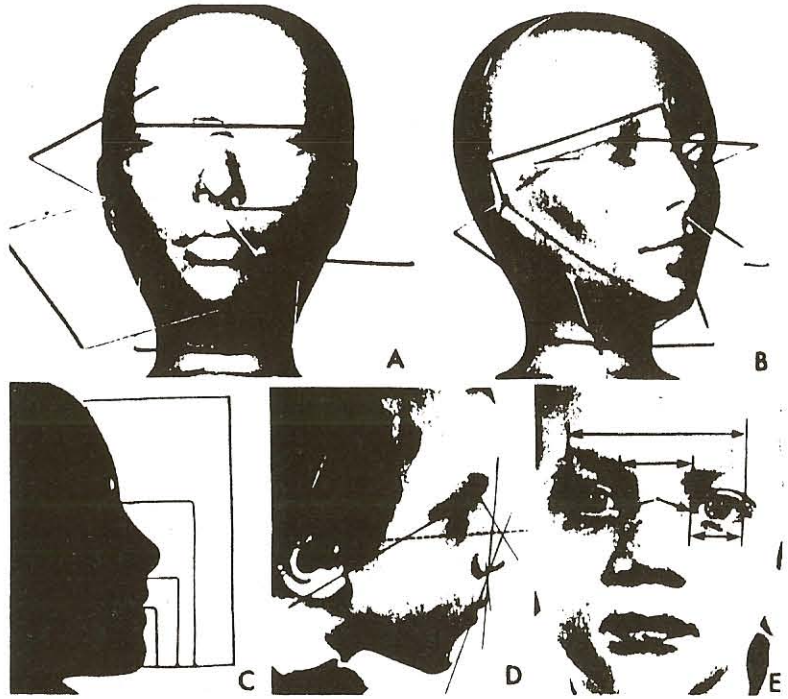


Fig. 2. Facial measurements. Antero-posterior (A), oblique (B), and lateral (C) views of head mold, showing some landmarks for taking measurements. (D) Lateral view of face, demonstrating some measurements. (E) Some ocular and interorbital measurements made on the 10 Caucasian patients.

with low-set ears, since the ear is the visual and actual reference point for measurement of the hairline. A peculiar maxillary fullness, which was not quantifiable, was noted in 10 patients.

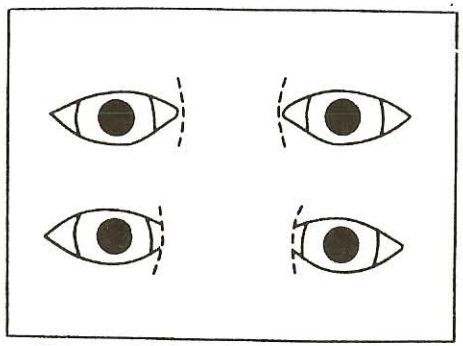
The photographic appearance complemented the physical findings and facial measurements in all 10 examined anthropometrically.

Carrying Angle

The normal range of the carrying angle is 14–15° in girls and 10–11° in boys [10]. The angle was abnormal in 4 of 7 girls measured (17° in one, 18° in two, and 20° in one) and in 5 of 9 boys (13°, 14°, 20°, 22°, and 35°). The angle was most abnormal in the three boys whose other manifestations were most severe.

Oral-Dental Assessment

Complete dental examination of 9 patients showed few specific aspects. The palate was highly arched in one and in another the teeth were flattened. The impression of relative smallness of the mandible was confirmed by cephalometry. The mandibular angle was steep and posterior facial height was reduced in 5 patients.



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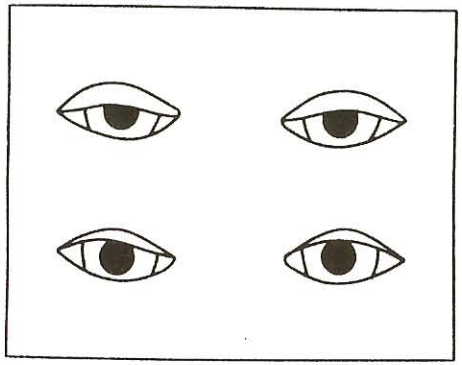

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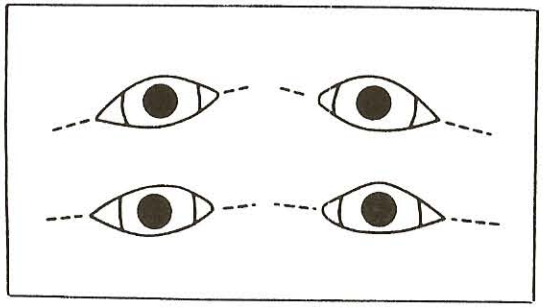

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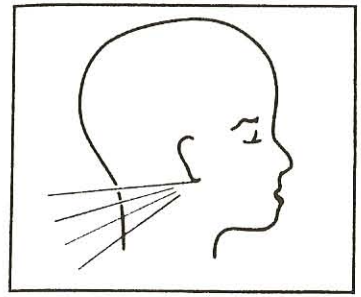
Fig. 3. Illustrations inserted in "scorecard" to aid in scoring physical abnormalities.



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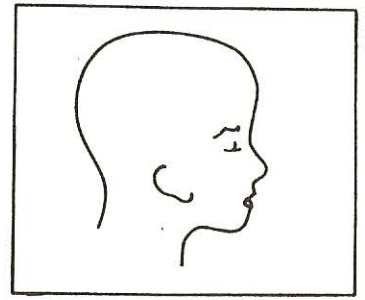

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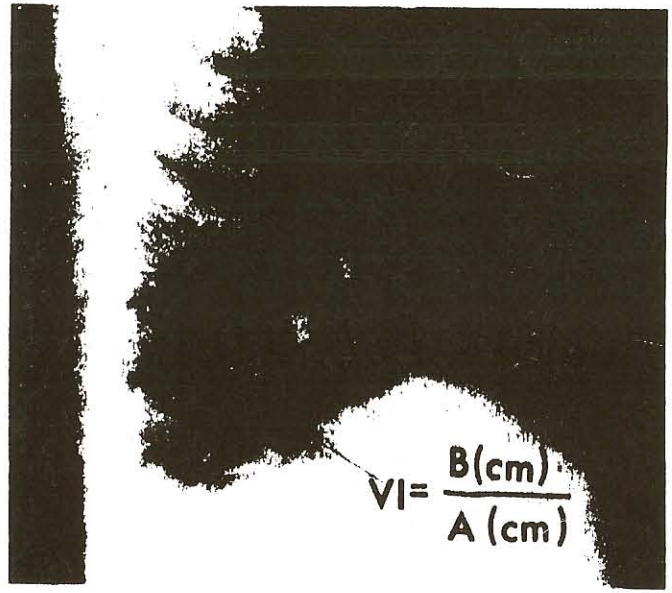

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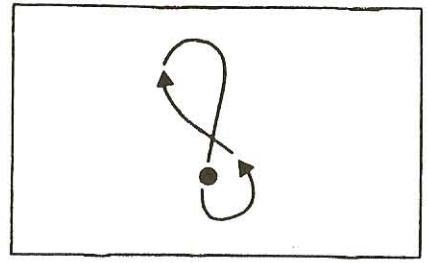

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Figure 3.

Formulation and Validation of the Scoring System

We correlated the data from our patients and the literature [1–4, 7, 11–14, 17–23, 26] to establish a scoring system for evaluating Noonan syndrome. For each aspect of the syndrome we assigned a maximum value according to the relative frequency of its occurrence (in the range of 2–15 points) and several values for scoring the degree of its abnormality in the individual patient. We then transferred the system to a scorecard, added line drawings illustrating visible defects (Fig. 3), and used the card to "score" each of our 23 patients.

The patients' scores, ranging from 15–84% (mean 46.7%, SD 16.4%) of the possible total, were less than 40% in 6, 40–49% in 3, 50–58% in 11, 71% in 2, and 84% in one. We considered scores of 50–59% suggestive and those of ⩾60% diagnostic of the Noonan syndrome.

We then tested the system by completing scorecards on 20 patients with normal facial appearance (group A) who had undergone cardiac catheterization for investigation of PS and four patients suspected of having Noonan syndrome who had been referred to the Hospital's Genetics Department for diagnosis (group B). The examiners did not know to which group the patients belonged.

Group A. No patient scored points for facial changes or other clinical signs of the syndrome. All scored for PS but none had a dysplastic valve or abnormal-appearing left ventricle. In none did the total score (mean 20% of possible total; range, 14–29%) indicate a diagnosis of Noonan syndrome.

Group B. Two patients had high scores (55% and 57%), and prior examination by the geneticists confirmed the diagnosis of the Noonan syndrome. The other two had low scores (22% and 29%); in these cases also, the geneticists' opinions concurred with our findings.

The sex of the patient and age at examination did not affect the application or accuracy of the scoring system.

DISCUSSION

Several authors have reported the occurrence of left ventricular abnormalities in Noonan syndrome, most notably Hirsch [14] who described asymmetric septal hypertrophy (ASH) in 9 of 28 patients with Noonan syndrome (another 8 had PS, 3 had left to right shunt, and 8 had a normal heart [20]). Of note in these patients with ASH was the absence of systolic anterior mitral motion despite a significantly thickened interventricular septum. In contrast, the only left ventricle abnormalities shown by echocardiography in our patients were nonspecific hypercontractility and septoposterior wall asynchrony, presumably a manifestation of right ventricular hypertension.

The typical eccentric hypertrophy revealed by left ventricular angiography correlated with unusual superior-axis deviation on scalar electrocardiograms. However, we have seen eccentric hypertrophy associated with mitral valve prolapse, atrioventricular canal, idiopathic hypertrophic subaortic stenosis, and other left ventricular anomalies.

Some observers think that the "cor cavus" deformity (Fig. 4) demonstrated by angiography is a nonspecific anomaly of the diaphragmatic portion of the left ventricular wall coupled with sympathetic elevation of the superoanterior surface. This eccentric thickening of the wall may be an artifactual image produced by bowing of the ventricular apex, rather than true muscular hypertrophy.

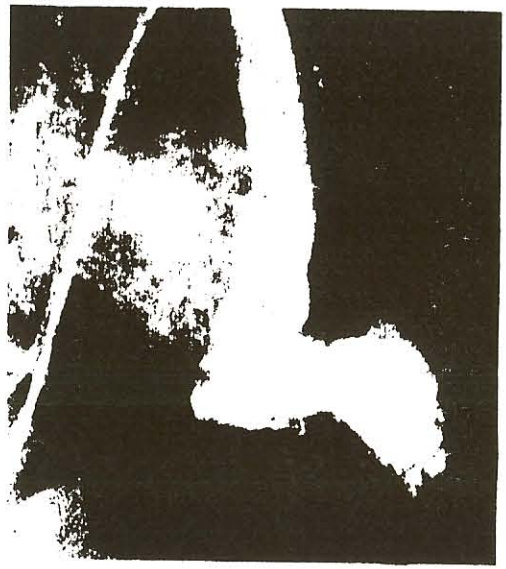

Fig. 4. Left ventricular angiogram performed in 60° right-anterior-oblique projection demonstrates the eccentric hypertrophy typical of Noonan syndrome.

Few references quantitate the pectus deformity. Backer's method is technically simple but is biased toward identifying severe cases requiring surgery for physical or cosmetic reasons. Thus, our patients who appeared clinically to have pectus excavatum would not come within Backer's category of "significant pectus."

Inclusion of the carrying angle in the scoring system proved valuable. The higher proportion of increased angles in males correlates well with the findings of Baughman [10]. These authors considered the variation attributable to chromosomal abnormality, but it may reflect only the phenotypic expression of the UTS since our patients who had an abnormal carrying angle had normal chromosomes.

The scorecard is simple to use. Anthropometry is not required since the line diagrams provide a guide for scoring each aspect by anthroposcopy. Unavailability of certain data (eg, information from catheterization or anthroposcopy in non-Caucasian patients for whom normal values have not been established) only slightly impaired the accuracy of diagnosis from the scorecard. Scores based on physical findings correlated well with those that included catheterization data.

The scoring system identified patients with Noonan syndrome, regardless of whether they had PS. Because predominant importance is assigned to physical aspects, the scoring system does not give false-positive scores for patients who have PS but not the Noonan syndrome. Thus, the 30–65% of patients who have the syndrome but no heart anomaly or heart defect other than PS (15–50%) [4, 7, 11, 13, 14, 17, 19–21, 24, 26, 29] should be identified with our scorecard.

In 1976, Preus and Fraser [30] described methods for establishing a diagnostic index for syndromes of unknown cause. They tested bimodal distribution patterns against a

group of normal controls. The index cases had Down syndrome by clinical examination and could, of course, be confirmed by karyotype. Clinical manifestations and supplementary data produced an accurate diagnostic discrimination in this group. The same technique was then applied to a group of patients with Brachmann-de Lange syndrome matched against normals. No definitive method exists for the diagnosis of the Brachmann-de Lange syndrome, but a similar bimodal distribution was found – although there was some overlap between groups.

We chose the figure of >50 as derived from the scorecard as suggestive of Noonan syndrome and ⩾60 as diagnostic. The data from our study did not suggest as clear a bimodal distribution as that of Preus and Fraser, but there was a distinct grouping towards very low scores or high scores. Only three patients fell into a "gray zone" (40–49) as an intermode.

The additional patients tested (groups A and B) clearly fell into a bimodal distribution with either very low scores or diagnostic ones. This application appears to support the value of utilizing a "multifactorial" approach to make a diagnosis for conditions having no single diagnostic feature.

SUMMARY

The diagnosis of syndrome without specific diagnostic test is to some degree subjective. As a result, the true incidence and natural history of such syndromes may not be determined, and many patients will fail to benefit when palliative or preventive measures become available. Use of a scoring system that incorporates a variety of features facilitates accuracy of diagnosis and reduces interobserver variation. We hope that use of the proposed scoring system will facilitate the evaluation of the Noonan syndrome as have similar systems for other conditions [30].

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Edited by John M. Opitz

APPENDIX

Scoring Instructions

*At least 20 characteristics must be scored; accuracy increases with the number of characteristics scored. A score ≥50% of the total possible indicates a high probability of Noonan syndrome. A score ≥60% of the total possible is diagnostic of Noonan syndrome.

Noonan Syndrome

Name _____

Scored* by DOB _____

_____, M.D. Sex _____

Characteristic	Degree of abnormality	Individual scores	Patient's score
A. General			
1. Stature	<3centile	5	
	<10centile	3	
	<25centile	2	
	>25centile	0	
2. Failure to thrive	Wt <3centile, milestones delayed	4	
	Wt <10centile, milestones normal	2	
	Absent (Wt >10centile, milestones normal)	0	
3. Mental retardation (estimated IQ)	Untrainable (IQ <50)	6	
	Trainable (IQ >50 <65)	4	
	Educable (IQ >65 <80)	2	
	Not retarded (IQ >80)	0	
4. Family history of Noonan syndrome	1 or more 1° relative	15	
	1 or more 2° relative	10	
	Possible 1° or 2° relative	5	
	No relatives affected	0	
B. Head and neck			
5. Hypertelorism (distance between inner canthi)	Greatly increased: >3 SD above 97centile	10	
	Increased: above >97centile	5	
	Absent (normal distance: 50–97centile)	0	
6. Epicanthic folds (Fig. 3a)	Bilateral, severe	6	
	Bilateral, mild	4	
	Unilateral	2	
	None	0	
7. Ptosis (Fig. 3b)	Bilateral, severe	8	
	Bilateral, mild	6	
	Unilateral, severe	4	
	None	0	
8. Start of palpebral fissure (Fig. 3c)	>10°	6	
	5–10°	3	
	No deviation		
9. Broad/high forehead	Hairline high, forehead appears bossed	4	
	Hairline normal, forehead appears bossed	2	
	Normal	0	

Characteristic	Degree of abnormality	Individual scores	Patient's score
10. Posterior hairline (in relation to plane of bottom of tragus (Fig. 3d)	Horizontal with plane	0	
	<10° below plane	2	
	>10–<20° below plane	4	
	>20° below plane		
11. Neck-webbing	Bilateral, severe	8	
	Bilateral, moderate	4	
	Unilateral, or mild bilaterally	2	
	None	0	
12. Upper lip	Protrudes markedly	4	
	Protrudes mildly	4	
	Normal	0	
13. Angle of mandible	Ascent to transverse rami >80°	2	
	Normal	0	
14. Fleshy fullness of maxilla	Severe	4	
	Moderate	2	
	Mild or none	0	
15. Nasal bridge	Very flat	4	
	Moderately flat	2	
	Somewhat flat or normal	0	
16. Ears (Fig. 3e)	Very low-set, rotated posteriorly	8	
	Moderately low-set, rotated posteriorly	6	
	Low-set *or* rotated posteriorly	4	
	Normal position	0	
C. Other skeletal characteristics			
17. Skeletal/thoracic vertebral index (Backer's formula) (Fig. 3f)	>97centile of predicted	5	
	90–97centile of predicted	2	
	Normal (for age)		
18. Pectus carinatum	Severe	4	
	Moderate	2	
	Absent	0	
19. Nipples appear widely spaced	Yes	2	
	No	0	
20. Clinodactyly (5th finger incurved and <80% length of 4th)	Bilateral, severe	4	
	Bilateral, mild *or* unilateral	2	
	Absent	0	
21. Cubitus valgus	a) Males: >15°	4	
	12–15°	2	
	<12	0	
	b) Females: >20°	4	
	17–20°	2	
	<17°	0	
D. Sexual characteristics			
22. a) Females: Menarche	After 14 yrs	5	
	At or before 14 yrs	0	
b) Males: Cryptorchidism	Bilateral	5	
	Unilateral	3	
	None	0	
E. ECG and VCG indices			
23. Marked right-axis deviation	Axis 150–260°	10	
	Any other	0	