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Noonan Syndrome:
Psychological and Psychiatric Aspects

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Although Noonan syndrome (NS) is a disorder with a relatively high prevalence, virtually no information in adult patients is available about the psychological and psychopathological profile. In the present clinical report the first series of 10 NS patients from an ongoing project is presented. The purpose of the study is to investigate the psychopathology, social cognition and adaptation as well as the quality of life in NS patients aged 16 years or more. *PTPN11* mutations were present in six patients and *KRAS* and *SOS1* in one patient, respectively. In two patients no known mutation was found. The results demonstrate a variable level of intelligence and suggest moderately impaired social cognition in terms of emotion recognition and alexithymia. In some patients mild signs of anxiety and lowered mood are found that, however, do not meet the criteria for a specific psychiatric disorder. It is concluded that NS in adults is associated with a behavioral phenotype in which deficiencies in social and emotional recognition and expression may be key elements.
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Key words: Noonan syndrome; social interaction; alexithymia; emotions; quality of life

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INTRODUCTION

Noonan syndrome (NS) is an autosomal dominant genetically heterogeneous disorder with an estimated incidence of 1:1,500 live births, although 60% of cases are reported to be sporadic [Shaw et al., 2007]. The description of the syndrome dates back to 1883 when Kobylinski reported on a male patient with several phenotypical characteristics. In 1963 Noonan and Ehmke were the first to define a specific group of patients, both male and female, with congenital heart defects, small stature, hypertelorism, skeletal malformations and mild mental retardation [Noonan and Ehmke, 1963]. As proposed by Opitz, this disorder was called Noonan syndrome (NS) [Opitz et al., 1965]. The diagnosis of NS is primarily clinical and can be made by using a scoring system listing major and minor congenital and morphological anomalies (see Table I) [Duncan et al., 1981; Van der Burgt et al., 1994].

NS should be considered when typical facial features are present as well as short stature, a variety of heart defects, particularly pulmonic stenosis and hypertrophic cardiomyopathy and skeletal deformations like pectus excavatum and carinatum. Additional features are cryptorchidism, lymphatic dysplasias, abnormal bleeding and a lower level of IQ [Tartaglia and Gelb, 2005; Van der Burgt, 2007].

In 1994 linkage analysis demonstrated that the gene for NS is located on the distal part of chromosome 12q [Jamieson et al., 1994]. Some years later it was found that missense mutations in the *PTPN11* gene (12, q24.1) account for about half of NS patients [Tartaglia et al., 2001, 2002]. Apart from this autosomal dominant form an autosomal recessive form, in which hypertrophic obstructive cardiomyopathy is more frequent, was suggested [Van der Burgt and Brunner, 2000].

The authors contributed equally to the present study.

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TABLE I. Diagnostic Criteria for NS

Feature	A = major	B = minor
1. Facial	Typical face	Suggestive face
2. Cardiac	Pulmonary valve stenosis and/or typical ECG	Other defect
3. Height	<3rd centile	<10th centile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First degree relative definite NS	First degree relative suggests NS
6. Other	All 3 (males): mental retardation, cryptorchidism, lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

[a]Definite NS: 1A plus one of 2A-6A or two of 2B-6B; 1B plus two of 2A-6A or three of 2B-6B.
Adapted from Van der Burgt et al. [Van der Burgt et al., 1994].

Given the overlap in congenital anomalies between NS and both cardio-facio-cutaneous syndrome (CFC) [Roberts et al., 2006a] and Costello syndrome (CS) [Hennekam, 2003], shortly after the discovery of mutations in the *HRAS* gene in the majority of patients with CS [Aoki et al., 2005] and in the *KRAS* gene in CFC [Niihori et al., 2006], germline mutations in *KRAS* gene were reported in a minority of patients with severe forms of NS [Carta et al., 2006; Schubbert et al., 2006; Zenker et al., 2007]. Most recently, a novel mutation in another gene involved in the RAS-MAPK pathway was discovered in a subset of patients with NS, the SOS1 [Roberts et al., 2006b; Tartaglia et al., 2007].

These disease gene discoveries have established NS and related traits (CFC and CS) as disorders of unregulated RAS-MAPK signaling [Tartaglia et al., 2007]. The RAS-MAPK pathway is implicated in growth-factor mediated cell proliferation and differentiation or cell death [Malumbres and Barbacid, 2003; Narumi et al., 2007].

Only limited data are available on the psychological and psychiatric characteristics of NS patients. As reported by several authors, in about one-third of the patients mild mental retardation is found. In most patients, however, the level of intelligence falls within the normal range [Allanson, 2005]. In 21 children with NS, aged 3–16 years, mood disturbances as well as social and communication problems have been found [Wood et al., 1995]. Van der Burgt et al. [1999] described lowered intelligence and planning problems in a group of 35 children. In a case report, inattention resembling features of an attention-deficit/hyperactivity disorder were suggested to be a key problem [Horiguchi and Takeshita, 2003]. By using a postal survey, in at least 30% of a group of 26 children, problems in social interactions were noticed [Sarimski, 2000]. In a group of 48 children aged 4–16 years, inattention and emotional problems could be observed [Lee et al., 2005]. Finally, Shaw et al. [2007] reported qualitative data on 112 adult Noonan patients, showing lack of social life, or an inability to fit in, although overall quality of life was evaluated to be satisfactory. Psychiatric disorders are rarely found and are described only in single case reports on patients with lower intelligence (Table II). Given the prevalence of NS, it is remarkable that virtually no reports have been published about classical psychiatric syndromes and that hardly any information is available about the cognitive and mental health status of adult patients with NS. As suggested earlier, this lack of information and the frequently described impaired social capacities may be the result of a relative deficit in the comprehension and expression of emotions [Verhoeven et al., 2004]. This can be illustrated as follows. Several authors have noticed difficulties with social competence, especially the emotional perception of self and others in patients with NS [Mahendran and Aw, 1969; Wood et al., 1995; Sarimski, 2000; Lee et al., 2005]. These phenomena are associated with social cognition, an umbrella term in which cognitive, emotional and motivational processes are involved to flexibly guide social behavior [Adolphs, 2001]. Examples can be found in the decoding of affective expressions in faces, voices and body postures, attribution of mental states to others (e.g., believes, desires, and intentions), and regulation of emotions [Van Rijn, 2007]. These processes can also be found in the concept of alexithymia, a historical, originally psychoanalytic concept, that gained renewed attention in neurocognitive research. "Alexithymia," or "no words for feelings", refers to an impairment of the ability

TABLE II. Psychiatric Syndromes in Patients With NS

References	Age, sex, IQ	Diagnosis
Mahendran and Aw [1969]	30, female, 68–70	Bipolar affective disorder
Rama Krishna et al. [1994]	37, male, 63	Schizophrenia
Paul et al. [1983]	4, male, 18 months[a]	Autistic disorder
Ghaziuddin et al. [1994]	13, male, 69	Autistic disorder
Verhoeven et al. [2004]	19, female, low	Panic disorder, alexithymia

[a]Developmental age.

to identify and communicate one's emotional state, in addition to diminished affect-related fantasy and imagery. There is rising evidence for a neural basis for this multidimensional construct [Aleman, 2005].

The present study was designed to investigate the psychiatric profile, cognitive qualities, social cognition and adaptation, as well as the quality of life in adult patients with NS.

MATERIALS AND METHODS

The study is part of an ongoing multidisciplinary project with the purpose to assess neuropsychological characteristics, social cognition, psychiatric symptoms and quality of life in patients with NS, aged 16 years or more. Patients volunteered after being invited by the Department of Human Genetics of the Radboud University Medical or the Dutch Noonan Syndrome Foundation and were subsequently referred to the outpatient Department for Neuropsychiatry of the Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands. All patients and their primary caregivers signed written informed consent to participate in this clinical project and to collect all data from the medical history. Screening for mutations was performed previously in the laboratory for DNA-diagnostics of the University Medical Center Nijmegen, The Netherlands.

During the first phase of the project, 10 patients were enrolled in whom the diagnosis NS was confirmed. Thereafter, a multidisciplinary evaluation took place in order to ascertain whether the research procedure was adequate to collect the required data.

In all patients an extensive neuropsychological assessment was performed followed by a neuropsychiatric examination using all available data from medical, developmental, and family history. Intelligence was measured using the Wechsler Adult Intelligence Scale (WAIS-III) [The Psychological Corporation, 1997], and the National Adult Reading Test (NART) [Nelson, 1982]. The Theory of Mind Test (TOM) was used to check if patients were able to interpret simple actions and intentions of other people [Steerneman et al., 2003]. In addition, Perrett's Emotion Recognition Task (ERT) was administered. This is a computer-generated paradigm for measuring the recognition of six basic facial emotional expressions (anger, disgust, fear, happiness, sadness, and surprise) presented at different intensities. Video clips of increasing length are presented, starting with a neutral face that changes into a facial expression of different intensity levels [Montagne et al., 2007]. Furthermore, because of the conceptual overlap between social cognition and alexithymia, we used two alexithymia questionnaires. The Toronto Alexithymia Scale (TAS-20) is an internationally used instrument to measure the ability to *give words to feelings* [Bagby et al., 1994]. The Bermond Vorst Alexithymia Questionnaire (BVAQ) was developed in the Netherlands. It offers the possibility to disentangle the so-called affective (arousal per se) and cognitive (recognizing, verbalizing, and analyzing emotions) aspects of alexithymia [Vorst and Bermond, 2001].

In order to gather psychometric information on the existence of psychopathology, the Structured Clinical Interview for the DSM-IV (SCID-I and SCID-II), and a Symptom Check List (SCL-90-R) were administered [First et al., 1997a,b; Arrindell and Ettema, 2003]. Finally, the Lancashire Quality of Life Profile (LQoL) was included, an interview widely used in Europe to measure health related quality of life variables [Van Nieuwenhuizen et al., 2001].

RESULTS

At present, 28 patients are referred. In Table III the clinical characteristics of the first series of 10 patients are depicted. The mean age and length (range) of the patients were 29.6 years (range: 16–59 years) and

TABLE III. Clinical Features of Patients With NS (n = 10)

Patient sex/age	Genetics	Heart defects	GH-treatment (years)	Bleeding anomalies	Pectus deform	Ptosis	Others
1, m/25	*PTPN11*	—	3	+	−	+	Cryptorchidism
2, m/59	Unknown[a]	PS	−	−	−	−	Hyperthyroidism
3, m/43[b]	*PTPN11*	—	−	−	+	−	Cryptorchidism
4, f/26	*SOS1*	PS	−	+	+	+	—
5, f/16	PTPN11	PS; ASD	−	+	+	+	—
6, m/56[b]	Unknown[a]	—	−	+	−	+	—
7, f/16	*KRAS*	MI	10	+	−	−	
8, f/19	*PTPN11*	PS	7	+	−	+	
9, f/17	*PTPN11*	PS; ASD	9	−	−	+	Pelvic lymphangiecta-sias/ lymphedema
10, m/19	*PTPN11*	PS	8	+	+	−	Neck lymphangioma; paresis obliquus sup; radio-ulnar stenosis; cryptorchidism

PS, pulmonic stenosis; ASD, atrial septal defect; MI, cleft mitral valve.
[a]Clinical diagnosis according to criteria Van der Burgt et al. [1994]. See Table I.
[b]Family load.

164 cm (range: 152–183 cm), respectively. As can be inferred from Table II, *PTPN11* mutations are present in six patients, *KRAS* and *SOS1* in one each, whereas in two patients (2 and 6) neither of the known mutations could be demonstrated. In these two patients the diagnosis was clinically confirmed by a geneticist, according to the diagnostic criteria proposed by Van der Burgt et al. [1994]. With respect to the level of intelligence, total IQ (WAIS-III) varied between 65 and 121. In six patients, a significant difference between verbal and performal IQ was found. Verbal capacities were better than performal in two patients and in the other four the reverse was found.

In one patient (1), a diagnosis of obsessive compulsive disorder was made previously and he was successfully treated elsewhere. In some patients, on a symptom checklist, mild signs of anxiety and lowered mood were found that, however, did not reach the intensity of a specific psychiatric disorder. None of the patients met the DSM-IV-criteria for Attention Deficit/Hyperactivity Disorder or Pervasive Developmental Disorder, albeit that in some patients subtle deficits in attention and concentration were demonstrated.

The results of the psychological test battery are depicted in Table IV. Social cognition, in terms of emotion recognition and alexithymia, appeared to be moderately impaired. Test results were suggestive for alexithymia, especially for its cognitive aspects (inadequate verbalization). A tendency was found towards an indirect expression of emotions during social interaction. In contrast with their self-report of psychological problems on the earlier mentioned checklist, and the evaluation of social functioning by significant others, patients reported average level of quality of life in terms of the LQoL domain satisfaction.

DISCUSSION

The results of the first phase of this project confirm the genetic and somatic heterogeneity and the variability in IQ scores in patients with NS. With respect to the SCL-90-R, a self-report instrument, high average scores (+1 SD) were found on complaints reflecting psychoneuroticism, anxiety and depression. The quality of life questionnaire, however, showed an average to high satisfaction with different aspects of life. Social and emotional recognition appeared to be slightly impaired which implies that some form of alexithymia is present.

An observation, never mentioned in publications on patients with NS, but made by all participating investigators of this project, is that they are in general remarkably friendly, cooperative and very willing to please. These are all aspects of a social desirable attitude. Social desirability can be defined as behavior guided by the environments' expectations [Paulhus, 2002]. As to the behavioral phenotype of NS, this could be a relevant neglected aspect of it. This may be reflected by the contrasting scores on the SCL-90-R and the LQoL which suggest a tendency towards desirable answering. The SCL-90-R could be a trigger for these patients to admit problems since its format only asks for confirmations of complaints.

TABLE IV. Neuropsychological Profile of Patients With NS (n = 10)

Measurement domain	Scale	Mean	SD	Performance
Intelligence	WAIS-III Total IQ	90	18.8	Low average
	WAIS-III Verbal IQ	88	20.6	Low average
	WAIS-III Performal IQ	93	18.6	Low average
	NART-IQ	90	11.8	Low average
Social cognition and adaptation	Emotion Recognition Task	2.1	0.3	Low average
	TAS-20 Total Score	45.3	8.6	Average
	BVAQ Total Score	120.9	12.5	Low
	BVAQ-Affective scale	45.4	9.2	Low average
	BVAQ-Cognitive scale	75.4	12.0	Low
	TOM	70.8	3.5	Low average
Psychopathology	SCID	One classification		
	SCL-90-R Psychoneuroticism	153.4	37.3	High average
	SCL-90-R Anxiety	17.7	4.4	High average
	SCL-90-R Depression	29.7	11.9	High average
Quality of life	LQoL Satisfaction with Leisure and Social participation	5.5	0.7	Average
	LQoL Satisfaction with Health	5.5	0.8	Average
	LQoL Satisfaction with Family relations	6.0	0.5	High average
	LQoL Satisfaction with Fulfillment of Life-goals	4.8	0.7	Average

Performance classification follows a five-point-scale in which each step represents one standard deviation; for example, "low" means 2 standard deviations from the normative mean of healthy subjects.
In the absence of applicable norms, TOM and LQoL performance classification represents clinical judgment.
WAIS, Wechsler Adult Intelligence Scale; NART, National Adult Reading Test; TAS, Toronto Alexithymia Scale; BVAQ, Bermond-Vorst Alexithymia Questionnaire; TOM, Theory of Mind Test; LQoL, Lancashire Quality of Life Profile.

Inherently, alexithymia and problems in social cognition, that is, in the ability to recognize and verbalize emotions, can lead to inadequate results on this kind of self-report measures, because they impose these very demands on the subjects studied. Therefore, during the rest of the project, alexithymia will also be measured *by proxy*, in that the questionnaires will be completed by significant others too.

In conclusion, although no behavioral phenotype has been suggested for NS, the results of the present project show that deficiencies in social and emotional recognition and expression may be key elements. The paucity in published cases with psychiatric syndromes might be an expression of a real lower incidence, or of an underreport in psychopathology in adult NS patients.

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