Health and Quality of Life in Adults with Noonan Syndrome

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Objective To obtain information on health and quality of life in adults with Noonan syndrome.

Study design From a cohort of 144 children with the diagnosis of Noonan syndrome whose height data had been published 23 years ago, 103 pediatric files providing adequate data were identified. Participants were sent questionnaires and asked to provide saliva for DNA analysis and to return for physical examination.

Results Ten of 103 individuals had died, 3 of them suddenly (standardized mortality ratio, 3.00; 95% CI, 1.44-5.52). Eighty-one individuals could be contacted by mail, with a positive response from 45. Genotyping in 36 of 45 participants revealed characteristic mutations in 61%. Median age at follow-up was 42.8 years. Mean adult heights were 169.2 cm (men) and 154.4 cm (women). In comparison with the general population, participants had lower educational status and lived more frequently without any partner. According to the response to the Short Form-36 questionnaire, quality of life was not impaired.

Conclusions Individuals with Noonan syndrome have higher mortality, lower education, and rarely partnership. Quality of life according to self-reported Short Form-36 was good. Men grew taller than previously reported from this cohort. *(J Pediatr 2012;161:501-5)*.

Noonan syndrome is a complex disorder mainly characterized by heart defects (stenosis of the pulmonary valve, hypertrophic cardiomyopathy), short stature, a typical face, pectus excavatum, carinatum, and mild impairment in intellectual abilities.[1,2] The prevalence of Noonan syndrome at live birth has been estimated to be 1 in 1000-2500 newborns.[2] The inheritance of Noonan syndrome is autosomal dominant in most of the familial cases, but more than half of the cases are sporadic due to de novo mutations. In approximately two-thirds of individuals with Noonan syndrome, a genetic cause can be determined. Heterozygous mutations of *PTPN11*, *SOS1*, and *RAF1* account for about 50%, 10%, and 5% of the cases, respectively.[3-5] Mutations in *KRAS*, *NRAS*, and *SHOC2* can occasionally be found.[6-8] These genes encode cytoplasmic signal proteins involved in several pathways including the Ras-mitogen-activated protein kinase pathway.[9]

Systematic studies on the health of adults with Noonan syndrome are rare.[10] There is one systematic study on morbidity and mortality of individuals with Noonan syndrome from Great Britain.[10] Short stature, the atypical face, reduced fitness because of cardiac disease, and reduced mental performance could be major obstacles influencing educational achievement, professional and social life, as well as quality of life. Therefore, parents of affected children should as reliably as possible be informed on the general long-term prognosis.

Methods

In order to evaluate outcome of adults with Noonan syndrome, we contacted the cohort of individuals with Noonan syndrome who had been recruited at our institutions 25 years ago and whose childhood height data had been the basis of the growth data for Noonan syndrome as reported in 1988.[11] These 144 children were born between 1952 and 1985. The median birth year was 1967. The restriction of the analysis to this historic cohort excluded ascertainment bias toward the chronically ill adult patient regularly seen in a clinic specialized in Noonan syndrome or toward the healthy and active adult being organized in a patient support group. In addition, the approach provided the excellent opportunity to contact individuals with a mean age above 40 years. The study protocol was approved by the Ethics Committee of the Medical Faculty of Tuebingen. The prospective study was started in June 2009 and was finished in January 2011.

Of the 144 patients reported in 1988,[11] file records could be identified in 116 cases. These file records were studied by one person. Data were extracted from the records in a standardized way including data on auxology, phenotypic characteristics, birth data, height of parents, heart defects, and additional diag-

BMI	Body mass index
PCR	Polymerase chain reaction
SF-36	Short Form-36
SMR	Standardized mortality ratio

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noses. Data on height at or closest to the age of 8 years were collected from the file records.

Thirteen file records did not contain the diagnosis of "Noonan syndrome" or "male Turner syndrome," nor was the description of the phenotype compatible with the diagnosis of Noonan syndrome. Therefore, these cases were excluded from the study. Of the 103 patients left for analysis, 10 patients had died. In 12 cases, the place of residence was not traceable. The remaining 81 individuals were contacted by mail. Finally, 45 patients (24 men) agreed to participate in the study (55.5% of the contacted persons) (**Figure 1**; available at www.jpeds.com).

A letter containing the invitation to the study, information material, the questionnaire, a measuring tape, a saliva collection tube, and a return envelope was sent to each participant. Persons were asked about educational status, profession, employment, marital status, parenthood, chronic illnesses, cardiac health, and chronic medication. This questionnaire contained almost exclusively closed questions and was created for this study. For the evaluation of quality of life, the validated German version of the Medical Outcome Study Short Form-36 (SF-36) questionnaire was used.[12] The SF-36 has 8 subscales: physical functioning (10 items), limitations on usual role-related activities due to physical health problems (4 items), bodily pain (2 items), general health (5 items), energy and fatigue (vitality) (4 items), social functioning (2 items), limitations on usual role-related activities due to emotional or mental problems (3 items), and emotional or mental health (5 items). The scores for each subscale range from 0 to 100, with higher scores indicating better health or function. All items refer to the subject's functioning during the past 4 weeks except those for physical functioning and general health, which relate to the time at which the form is completed. For comparison, we used data from a German reference population aged 31 to 50 years.[12]

In addition, participants were asked to measure weight and height by themselves. For height determination, a metallic measuring tape and a detailed instruction for use in a standing height position with the help of a second person were provided. The pediatric data from the 1970s and 1980s on growth, heart disorder, puberty development, and minor abnormalities were added to the data set collected. The height SDS was calculated as follows: individual height in centimeters minus mean height of the sex- and age-matched reference according to Prader et al[13] divided by the SD of this reference.

For genetic testing, we used the Oragene (OG-500) DNA collection kit (DNAgenotek, Ottawa, Ontario, Canada). DNA was extracted from saliva samples collected by use of the Oragene-DNA sample collection kit (DNA Genotek Inc, Kanata, Ontario, Canada) according to the manufacturer's instructions. All 15 coding exons and flanking intronic portions of *PTPN11*, as well as all exons containing known mutations of the genes *SOS1*, *RAF1, KRAS, NRAS,* and *SHOC2,* were screened for mutations using high-resolution melting analysis on a LightCycler 480 Real-Time PCR [polymerase chain reaction] System (Roche Diagnostics, Grenzach-Wyhlen, Germany). Oligonucleotide primer sequences and protocols are available on request. PCR products showing abnormal melting curves were further analyzed by direct sequencing of PCR products using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, California) and an automated 24-capillary 3500xL Genetic Analyzer (Applied Biosystems).

During the physical examination of 20 participants (13 men) at the University Children's Hospitals in Tuebingen and Goettingen (by G.B. and C.F.), the presence of syndromic features, clinical signs of hypogonadism, and cardiac function were studied. Clinical data were documented in detailed case report forms.

Statistical Analysis

Percentages of various characteristics in both the patients with Noonan syndrome and the age-related German general population are reported. Exact binomial 95% CIs were calculated for the patient sample proportions, and the differences in the proportions were tested using the χ^2 test. The standardized mortality ratio (SMR) with 95% CI was calculated considering age, sex, and calendar year with reference to the national vital statistics supplied by the German Federal Statistical Office. Exact 95% CIs were constructed directly from the Poisson distribution. The statistical analysis was performed with the JMP 8.0.2 statistical software (SAS Institute, Cary, North Carolina).

Results

Mean age at assessment of the total cohort of 45 participants (24 men) was 42.1 years (median age 42.8 years, range 25.0-57.7 years). The mean follow-up interval was 31 years. Analysis of the childhood characteristics of the participants (n = 45) and contacted subjects who did not take part (n = 36) did not reveal any differences (**Table I**; available at www.jpeds.com). According to the patients' files, valvar pulmonary stenosis had been recorded in 31 (69%) study participants and hypertrophic cardiomyopathy in 5 (11%) study participants. Of the 36 (61%) participants tested, 22 were carriers of characteristic mutations involved in Noonan syndrome (**Table II**; available at www.jpeds.com). The only novel mutation found was the L261F *PTPN11* missense mutation changing a highly conserved amino acid in the immediate neighborhood to the known mutations L262F and L262R.

The main auxological characteristics of the 45 adult study participants (24 men) obtained by questionnaire are summarized in **Table III** and **Figure 2**. The mean final height of the women with Noonan syndrome was 154.4 cm (−1.73 height SDS, Prader reference). In men, mean final height was 169.2 cm (−1.27 height SDS, Prader reference). Three men had an *SOS1* mutation (12.5% of all men). None of the participants had been treated with human or recombinant growth hormone. In comparison with the mean height SDS at or closest to the age of 8 years, spontaneous gain in height occurred with a mean gain of +0.57 SDS in boys and