Noonan Syndrome

First description: The first description of Noonan syndrome (NS) dates back to 1883, when a student named Kobylinski reported on a male patient with several phenotypical characteristics. In 1963, paediatric cardiologists Dr. Jacqueline Noonan and Dorothy Ehmke were the first to identify NS as a distinct syndrome in both male and female patients, with congenital heart defects, small stature, typical faces, skeletal malformations and mild mental retardation (Noonan & Ehmke, 1963; Noonan, 1968). John Opitz, one of Dr. Noonan's students, suggested the eponym and confirmed NS as a nosologic entity.

Associated conditions: NS is a genetically heterogeneous disorder, with different causative mutations in the RAS-MAPK pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome), Noonan syndrome-like disorder with loose anagen hair (NSLH), and CBL-associated syndrome. They are grouped into the neurocardiofacialcutaneous syndrome family, or the Ras-opathies (Tartaglia et al., 2011).

In the past, Noonan syndrome has -incorrectly- been referred to as 'Male Turner syndrome', 'Female pseudo-Turner syndrome', 'Turner phenotype with normal karyotype', 'Ullrich-Noonan syndrome' and 'Pterygium Colli Syndrome, included'. Although the NS phenotype has resemblance to the phenotype of (Ullrich-)Turner syndrome, the genotypes differ. Other syndromes with different genotypes but some phenotypical similarities to NS are William's syndrome and Aarskog syndrome (Van der Burgt, 2007).

Genetics and molecular biology: NS may occur on a sporadic basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission. In approximately 50% of the patients a missense mutation is found in the *PTPN11* gene on chromosome 12 (12q24.1). Germline mutations in twelve other genes of the Ras-MAPK pathway have been identified as causative in NS and closely related disorders: *SOS1* (about 10% of the cases), *RAF1* (5-15%), *KRAS* (<2-5%), *NRAS* (<2-5%), *BRAF* (<2%), *SHOC2* (<2%), *MAP2K1 (MEK1)* (<2%), *MAP2K2, CBL* (<1%), *RIT1* (<1%), *A2ML1* (<1%), *SPRED1,* and *HRAS*. In about 25% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Pasmant et al., 2009; Tartaglia et al., 2011; Aoki et al., 2013; Vissers et al., 2015).

Incidence/prevalence: The incidence of NS is estimated between 1 in 1000 to 1 in 2500 live births (Allanson, 2010).

Physical features and natural history: Key characteristics are 1) short stature, 2) typical facial dysmorphology (wide-spread eyes, drooping eyelids, and low-set, posteriorly rotated ears with a thickened helix) and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial septal defect). Some additional features are hematologic and ectodermal anomalies, skeletal anomalies, lymphatic dysplasia, cryptorchidism, and a webbed neck. Neonatal feeding difficulties and failure to thrive are present in the majority of infants with NS. Phenotypical expression is highly variable and often milder in adulthood than in youth. The diagnosis is primarily made on clinical grounds, by observation of cardinal features. The most widely used scoring system was developed in 1994 and updated and validated in 2010 (Van der Burgt et al.,1994; The Noonan Syndrome Guideline Development

Group, 2010). Life expectancy for patients with NS is fairly normal, unless there are major complications of heart disease. Premature delivery is the main source of morbidity.

Behavioural characteristics and psychopathology: A distinctive pattern of behavioural characteristics can not be recognised, although there are some indications for an increased risk for behavioural problems in children, characterised by social problems, stubbornness, restlessness, and impulsivity. Traits from the autism spectrum and ADHD symptoms have been reported in children with NS in comparison with their nonaffected siblings (Adviento et al., 2013; Pierpont et al., 2015). Classical psychiatric syndromes have only incidentally been described for NS and mainly concern cases of anxiety disorders, obsessive-compulsive disorders, and mood disorders. In adults, alexithymic traits seem to be present more often, as well as elevated levels of psychological and social distress (Verhoeven et al., 2008; Wingbermühle et al., 2009; 2012a). In comparison with women with Turner syndrome alexithymia and impairments in emotion recognition seem to be less pronounced (Roelofs et al., 2015).

Neuropsychological characteristics: Neuropsychological findings show intelligence scores in a wide range, with a mildly lowered average intelligence. Language and motor development are often delayed. In children, a highly variable cognitive profile has been found, with indications for impairments in visual processing and language development, weaknesses in memory function (inconclusive results mention problems in working memory, long-term verbal memory and immediate visual memory), mild deficits in selective and sustained attention, and suboptimal planning and organisational skills (Wingbermühle et al., 2009; Alfieri et al., 2011a,b; Pierpont et al., 2010; 2013; 2015). These cognitive impairments may explain learning problems and an increased need for special education.

While extensive cognitive problems seem to be present in childhood, cognition in adults with NS is mainly characterised by a lowered speed of information processing. As described above, social cognitive functions (recognising and expressing emotions) may be impaired as well (Wingbermühle et al., 2012b).

Available management guidelines:

The Noonan Syndrome Guideline Development Group (2010). *Noonan Syndrome Clinical Management Guidelines.* Dyscerne, University of Manchester.

More information

For information on NS in OMIM, online database of human genes and genetic disorders, see: http://www.ncbi.nlm.nih.gov/omim/163950. For details on the Noonan syndrome support group, see: www.noonansyndrome.org.

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