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 developmental delay (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 Cardiofaciocutaneous (CFC) syndrome, Costello syndrome (CS), Legius syndrome (LS), Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (NS-ML; formerly called LEOPARD syndrome), and Noonan syndrome-like disorder with loose anagen hair (NS-LAH). They are grouped into the neurocardiofacialcutaneous syndrome family, or the RASopathies (Tartaglia et al., 2011, Tajan et al., 2018).

Genetics and molecular biology

NS is most often inherited in an autosomal dominant manner, although NS caused by a pathogenic variant in *LZTR1* also can be inherited in an autosomal recessive manner. In 60% of patients with autosomal dominant NS, the condition is caused by a de novo mutation. In approximately 50% of patients with NS a missense mutation is found in the *PTPN11* gene on chromosome 12 (12q24.13). Germline mutations in 16 other genes of the RAS-MAPK pathway are associated with NS and closely related disorders: *SOS1* (10-13% of the cases), *RAF1* (5-10%), *RIT1* (5%), *KRAS*, *NRAS*, *MRAS, BRAF*, *SHOC2*, *CBL*, *SOS2*, *RRAS*, *RASA2*, *MAP2K1, MAP2K2*, *LZTR1*, and *PPP1CB*. In about 20 to 30% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Allanson & Roberts, 2019; Grant et al., 2018; Liao & Mehta, 2019; Motta et al., 2020). Apart from these, preliminary evidence points at several other candidate genes such as *RREB1* (Grant et al., 2018; Kent et al., 2020).

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 and down-slanting eyes, drooping eyelids, and low-set, and posteriorly rotated ears with a thickened helix), and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial septal defects are most common). Some additional features are variable developmental delay, neonatal feeding difficulties, failure to thrive, hematologic and ectodermal anomalies, skeletal anomalies (e.g., chest deformity), lymphatic dysplasia, cryptorchidism, ocular abnormalities, widely spaced nipples, and a webbed neck. However, these characteristics are not seen in all patients with NS, phenotypical expression is highly variable and often milder in adulthood than in youth (Allanson & Roberts, 2019; Noonan, 2005). 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; DYSCERNE-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 indications for an increased risk for behavioural problems in children, mostly characterised by social problems (e.g., social immaturity, diminished insight in social situations, impaired social skills), attentional problems, hyperactivity, and impulsivity (Pierpont, 2016; Pierpont et al., 2018; Wingbermühle et al., 2012a). Autism spectrum traits and ADHD symptoms seem to be more frequent than in the general population (Pierpont, 2016). There are indications that mood and anxiety problems, emotion regulation difficulties, and social distress are more common in children and adults with Noonan syndrome (Alfieri et al., 2021; McNeill et al., 2019; Pierpont 2016; Wingbermühle et al., 2012a). Higher levels of introversion and alexithymia (problems in the identification and verbalisation of own emotions) in adults with NS are thought to contribute to internalising symptomatology (Roelofs et al., 2019).

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, varying reports of memory problems, attention problems, and suboptimal planning and organisational skills (Pierpont 2016). These cognitive impairments might explain the anecdotally reported learning problems and need for special education. While cognitive problems are frequently 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 guidelines for assessment/treatment/management

The specific problems that patients with NS may encounter in daily life appear to result from a complex interaction between genetic, somatic, cognitive, psychological, and environmental factors. Therefore, a multidisciplinary approach and intensive collaboration between clinical geneticists, cardiologists, paediatricians, clinical neuropsychologists, physiotherapists, and speech therapists, among others, is necessary to treat patients with NS as best as possible. Moreover, NS is a lifelong developmental disorder, which poses different challenges in different stages of life. Repeated individual clinical and neuropsychological assessment is advised throughout the lifespan, especially at crucial moments in the development and when problems occur. The recommended multidisciplinary approach and life-long follow-up may be formalised in centres of expertise for patients with NS and other RASopathies. Specific recommendations for the management of patients with NS at different stages of their lives can be found in the international clinical guidelines on Management of Noonan syndrome from the Noonan Syndrome Guideline Development Group (DYSCERNE, 2010).

More information

- www.ncbi.nlm.nih.gov/omim/163950 For the information on NS in OMIM, an online database of human genes and genetic disorders.
- www.noonansyndrome.org.uk For the Noonan syndrome support group Inc.
- rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf For the Noonan Syndrome Clinical Management Guidelines.

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