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SPECIAL REVIEW

Marathon of eponyms: 14 Noonan syndrome

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The use of eponyms has long been contentious, but many remain in common use, as discussed elsewhere (Editorial: Oral Diseases. 2009: 15; 185). The use of eponyms in diseases of the head and neck is found mainly in specialties dealing with medically compromised individuals (paediatric dentistry, special care dentistry, oral and maxillofacial medicine, oral and maxillofacial pathology, oral and maxillofacial radiology and oral and maxillofacial surgery) and particularly by hospital-centred practitioners. This series has selected some of the more recognised relevant eponymous conditions and presents them alphabetically. The information is based largely on data available from MEDLINE and a number of internet websites as noted below: the authors would welcome any corrections. This document summarises data about Noonan syndrome.

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Also known as

Familial Turner syndrome
Female pseudo Turner syndrome
Pseudo Turner syndrome
Male Turner syndrome
Pseudo Ullrich–Turner syndrome
Turner-like syndrome
Turner phenotype with normal karyotype
Turner phenotype syndrome
Turner syndrome in female with X-chromosome
Ullrich–Noonan syndrome
XX and XY Turner phenotype syndrome

The condition

A class of developmental disorders caused by dysregulation of the Ras-induced mitogen-activated protein kinase (MAPK) signalling pathway (the Ras-MAPK pathway) is now recognised. This signalling pathway starts with activated Ras, which activates the protein kinase activity of RAF kinase which then phosphorylates and activates MEK (MAPK or extracellular signal-regulated kinase). Then MEK phosphorylates and activates MAPK. MAPK eventually affects microtubule associated proteins. The Ras-MAPK pathway is thus essential in the regulation of the cell cycle, differentiation, growth and senescence.

Three of these developmental disorders – Noonan (NS), Costello (CS) and cardio-facio-cutaneous (CFC) syndromes – have overlapping features characterised by a distinctive phenotype of facial dysmorphia, cardiac defects, musculoskeletal and cutaneous abnormalities and neurocognitive delay.

Noonan syndrome often maps to chromosome 12q. Approximately half the patients with NS carried a mutation of the PTPN11 (protein tyrosine phosphatase, non-receptor type 11) gene at that location, which encodes protein tyrosine phosphatase SHP-2 – a component of several signal pathways involved in embryonic development that modulate cell division, differentiation and migration, including that mediated by epidermal growth factor receptor (EGFR). The latter pathway is important in the formation of the cardiac semilunar valves. PTPN11 gene mutations can also cause Noonan-like multiple giant cell lesion syndrome, or the LEOPARD syndrome. Also called multiple lentigines syndrome (lentigines are brown skin spots similar to freckles), LEOPARD syndrome consists of lentigines, ECG abnormalities (measurement of abnormal electrical heart activity), ocular hypertelorism (widely spaced eyes), pulmonary stenosis (narrowing of the artery from the heart to the lungs), abnormalities of genitalia (reproductive organs), retardation of growth (short stature) and deafness.

Activating mutations in SOS1 can also give rise to NS. SHP-2 and SOS1 both act as positive regulators of the Ras-MAPK pathway. Additional mutations in KRas, RAF1 and MEK genes have been reported in some cases of NS.

There is no simple rule to readily distinguish NS from CFC. The main phenotypical features also suggest significant clinical overlap between CFC and CS.

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Because of its particular cancer risk, the term 'Costello syndrome' should only be used for patients with proven H-Ras mutation.

Noonan syndrome is a relatively common (1:1000) familial autosomal dominant syndrome similar to Turner syndrome, with the Turner phenotype, but NS occurs in both genders and there is no gross chromosomal defect. Clinical features of NS are short stature, low-set ears, minor skeletal deformities (especially pectus excavatum and cubitus valgus), gastrointestinal, genitourinary abnormalities and impaired haemostasis (thrombocytopenia and partial defects in Factors VIII, IX and XII), and intelligence is often below average. NS is one of the most common genetic syndromes associated with congenital heart disease: cardiac abnormalities, which occur in 50% of patients, include pulmonary valve stenosis, thick and dysplastic pulmonary valves, right heart anomalies and left ventricular cardiomyopathy. Characteristic craniofacial features of NS include the following:

- Large head
- Short neck, webbed neck (pterygium coli), with low hairline and excess skin on the back of the neck
- Triangular face shape, with broad forehead
- Hyperteleorism, with mild antimongoloid slant
- Ptosis (unilateral or bilateral), epicanthal folds and exophthalmos
- Strabismus (squint)
- Small, upturned (saddle) nose
- Deeply grooved philtrum
- Low-set fleshy ears, with helix distortion
- Micrognathia
- High arched palate
- Bifid uvula and occasional cleft palate
- Poor tongue control.

Despite identification of four causative genes, the diagnosis of NS is still based on clinical features. In her paper of 1968, Noonan wrote also that one or both parents frequently showed one or more characteristics of NS. Disorders to be differentiated include Turner, LEOPARD and foetal alcohol syndromes.

Background to eponym

An early description of the Noonan syndrome is credited to Koblinsky (1883), a medical student at the Russian/Estonian University of Dorpat. The phenotype was also documented by Weissenberg in 1928. Jacqueline Noonan and Dorothy Ehmke (cardiologist) in 1963 defined clinical and cytogenetic findings in nine children with valvular pulmonary stenosis, short stature, hypertelorism and skeletal anomalies. Noonan in 1968 described 19 patients with unusual facies, congenital heart defect and other symptoms resembling those of Turner's syndrome, but with grossly normal chromosomes.

The term Noonan's syndrome was suggested in 1965 by John Marius Opitz in a paper at the Society for Pediatric Research.

The main person

Jacqueline Anne Noonan was born on 28 October 1921, in Burlington, Vermont, USA and, graduated in chemistry at Albertus Magnus College, New Haven, in 1950, and then in Medicine from the University of Vermont in 1954. She worked at Memorial Hospital, University of North Carolina, before training in paediatrics at the Children's Hospital in Boston. In 1959 she was appointed paediatric cardiologist at the University of Iowa. In 1961 she moved to a subordinate professorship at the University of Kentucky, becoming Professor in 1969. From 1974 she was chairman of their Department of paediatrics. In 1971 she was honoured with the Helen B. Frazer Award, in 1985 with Harpers Bazaar's Best Women Doctors in America and later with The Best Doctors in America award.

Associated persons

Jacqueline Anne Noonan
Otto Ullrich

Source internet sites (accessed 21 February 2009) and further reading

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