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Noonan syndrome: About two observations

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Abstract

Noonan syndrome is an autosomal dominant multisystemic genetic disorder in which most cases are sporadic. It affects 1/1000 - 1/2500 individuals without gender predominance. It is characterized by facial dysmorphia, short stature, congenital heart disease, skeletal malformations and delayed acquisition. The diagnosis is essentially clinical. Our work reports two observations of Noonan syndrome collected in the department of pediatrics II, at the children's hospital Rabat during 3 years (from January 2015 to December 2018). They are a boy and a girl, the average age at the onset of symptoms and genetic diagnosis were respectively 2.5 years and 4 years. In our two patients, there was first-degree consanguinity. The manifestations that led to the diagnosis were a characteristic facies in 100% of the cases; statural delay in the 2 patients (100%); cryptorchidism in one patient (50%), The SN was genetically confirmed in 1 patient (50%) by identifying a mutation of the PTPN11 gene.We illustrate through these observations the different phenotypic expressions of the SN, as well as its clinical, paraclinical, therapeutic and evolutionary approach by insisting on the need for a multidisciplinary collaboration in order to ensure to the bearers of this syndrome a better life quality.

Keywords: Dysmorphia, Syndrome, PTPN11

Introduction

Noonan syndrome is a rare, highly variable and multisystemic disease, mainly characterized by short stature, characteristic facial dysmorphia, congenital cardiac anomalies, cardiomyopathy and an increased risk of developing tumors in childhood, there is sometimes an intellectual deficit and delayed language acquisition. It was first described by the cardiopediatrician Jacqueline Noonan in 1963 and is due to a mutation of the gene called PTPN11 (Proteine-Tyrosine Phosphatase Nonreceptor-Type 11), located on chromosome 12, more recently, mutations of the K-RAS gene have been identified in a few patients with Noonan syndrome (approximately 5%). We illustrate through these 2 clinical observations the clinical aspects, diagnostic means and the therapeutic and evolutionary management of patients with this syndrome.

Patients and observations

Observation 1: 4 year old child; female, from a pregnancy followed to term with a birth weight of 1500 grams, apgar: notion of delayed cry, having as antecedent a hospitalization in neonatal period for respiratory distress, notion of death in the siblings: the first death at h2 of life in a table of malformation and the second death at the age of 10 months by severe respiratory distress. Notion of 1st degree consanguinity and notion of psychomotor delay. Followed in consultation of dysmorphology for a statural delay with a dysmorphic syndrome and generalized convulsions; the clinical examination found a dysmorphic facies with low implanted ears, spread eyes and small neck, widened forehead and ptosis; a staturo weight delay: weight 16 kg (-1DS) and height (-2DS) ,a cerebral CT was requested returned normal ,the EEG showed a normal background activity with spikes in left fronto temporal ,a TSH came back normal ,the diagnosis of noonan syndrome was evoked from where a genetic study was requested which showed the presence of the familial mutation p. Asn58Asp(c.172 A>G) at the level of exon 3 of the PTPN11 gene in heterozygous state which confirmed the diagnosis, an echocardiography made normal, the visual and auditory evoked potentials were requested returned normal. The child was put under depakine with a good clinical evolution.

Observation 2 : 3 year old male child, from a pregnancy carried to term with a notion of neonatal suffering and a notion of first degree consanguinity, hospitalized during the neonatal period for respiratory distress. Followed in consultation of dysmorphology for a congenital nystagmus with statural delay, the clinical examination finds a macrocrania, cranial perimeter to (+2DS), right testicular ectopy, a statural delay t (-3 DS), short limbs and a short neck, hypertelorism and micrognatia. A transfantanellar ultrasound showed no abnormalities, brain MRI revealed bilateral and asymmetrical signal abnormalities of the frontal and occipital white matter in favor of a leukopathy falling within the framework of the noonan syndrome, EEG showed a normal tracing, bone age is 8 months, IGF1 was normal, anti-transglutaminase antibodies negative, TSH us normal. The diagnosis of noonan syndrome was evoked in front of the statural delay ; the dysmorphic syndrome and the testicular ectopia and therefore a genetic study was requested having shown the absence of mutations at the level of exons 3 and 8 of the PTPN11 gene; the diagnosis of noonan syndrome was retained even in absence of genetic argument; the echocardiography made returned normal; the visual and auditory evoked potentials returned normal. The child was operated for testicular ectopy and benefited from several sessions of orthopedic rehabilitation.

Patient 1 : noonan syndrome with a dysmorphic facies : low-implanted ears, wide-set eyes ,small neck, widened forehead and ptosis.

Patient 2 : noonan syndrome with short limbs, short neck, hypertelorism and micrognatia.

Discussion

Noonan syndrome (NS) is an autosomal dominant genetic disorder characterized by a distinctive phenotypic triad : craniofacial dysmorphic features, congenital heart disease, and short stature ; it is a relatively common disorder with an estimated incidence of 1 in 1,000 to 2,500 live births ; it affects both sexes equally : the sex ratio H= F [1].

Craniofacial features are characterized by a distinctive facies that changes over time, with features that are more striking in children becoming less prominent in adulthood [2]. The characteristics are a triangular face shape (enlarged forehead), hypertelorism, ptosis, strongly arched diamond-shaped eyebrows, nose with flattened bridge and bulbous tip, short neck, poorly developed cheekbones, thick ears tilted backwards, with a protruding lobe; ogival shaped palate. Teeth are sometimes poorly implanted and micrognathia [3]; dysmorphic syndrome was present in our 2 patients.

Cardiovascular manifestations, The prevalence of cardiovascular abnormalities is estimated at 70% - 80% of cases [4,5]. A wide spectrum of abnormalities has been described, the most common being pulmonary stenosis, usually associated with valvular dysplasia (50% -60%), hypertrophic cardiomyopathy (20%) [6], usually detected early in life, atrial septal defects (6% - 10%) and ventricular septal defects, pulmonary artery branch stenosis, coronary artery defects, coarctation of the aorta and, less frequently, tetralogy of Fallot and patent ductus arteriosus. The literature also describes electrocardiographic abnormalities in these patients (50%). [7] These are often wide QRS intervals, arrhythmias are infrequent [8]; we note the absence of cardiovascular involvement in our study, ETT returned normal in our 2 patients.

Nutritional aspects and disturbances of energy homeostasis, during the neonatal period, infants with NS present feeding difficulties with weak sucking, sporadic episodes of nausea and vomiting, (25%), and gastroesophageal reflux. These symptoms usually improve or disappear completely by 15 months of age [9,10]. Several studies have described a trend toward low body weight not only in the early years of life, but throughout life. An animal model with the p. Thr468Met genetic variant (characteristic of NS-ML) with a metabolic phenotype characterized by defective adipogenesis, increased energy expenditure and mitochondrial activity, increased insulin sensitivity, and resistance to the effects of an obesogenic diet [11]. These findings are unclear, although future research will likely uncover more information about these disturbances in energy homeostasis.

Renal and urogenital manifestations, Cryptorchidism has been described in 60% to 80% of male patients with NS [9]. Several studies have reported elevated levels of luteinizing hormone (LH) and follicle stimulating

hormone (FSH) and decreased levels of inhibin B and anti-mullerian hormone (AMH) in patients with NS compared to the general population, the literature also describes a higher frequency of infertility in male patients with NS. In contrast, it appears that females with NS have normal fertility (which would explain why maternal transmission predominates in familial cases). Renal abnormalities are present in 10% of cases (solitary kidney, pyeloureteral stenosis and dilatation of the renal pelvis) [12]; in our patients, cryptorchidism was noted in one patient and renal ultrasound was normal in both patients.

Hypothyroidism and autoimmune diseases, most studies have found a higher incidence of autoimmune thyroiditis in patients with NS compared to the general population[10], Other features described in the literature include celiac disease, systemic lupus erythematosus, vitiligo and anterior uveitis ; For our patients, autoimmune thyroiditis was eliminated, TSH was requested and returned normal in both patients and anti-transglutaminase antibodies requested in one patient returned negative.

Impact on growth and development. Prenatal growth is generally unaffected [13], children with NS show a pattern of postnatal growth retardation characterized by, delayed puberty with attenuated growth spurts and an adult height approximately 2 standard deviations (SD) below average. Delayed puberty is common, with a mean age of onset of puberty of 13.4 years (10.8 - 16.4 years) in boys and 13 years (10.9 - 15 years) in girls. There is a mean delay in bone age of 2 years. Some authors have found hormonal profiles suggestive of growth hormone deficiency in NS patients, with decreased levels of insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP-3) and responses to stimulation with growth hormone in the upper limit [14]. Other studies suggest that hyperactivation of RAS-MAPK may affect chondrocyte differentiation during bone growth by a mechanism independent of IGF1 [15]. In our study, one of our patients, as described in the literature, had a delay in bone age of 3 years, but the IGF1 dosage was normal, so the statural delay in this patient can be explained by the hyperactivation of RAS-MAPK affecting the differentiation of chondrocytes during bone growth by a mechanism independent of IGF1.

Musculoskeletal anomalies, thoracic deformities (with pectus excavatum below and spectus carinatum above) occur in 70% to 95% of cases, possibly accompanied by ulna valgus, genu valgum [16], scoliosis (10% - 15%) or other less frequent deformities of the spine, such as kyphosis, spina bifida or malformations of the vertebrae or ribs. Joint hypermobility is also common [10]. There is evidence that overall bone mineral density in children with NS is lower than controls matched for age-, sex-, height- and ethnicity-. However, the incidence of fractures in children does not appear to be higher compared with the general population, The incidence of fractures in adults with NS is unknown, and therefore the clinical relevance of these findings is unclear and must be established by longitudinal studies. Musculoskeletal abnormalities were absent in our 2 patients.

Lymphatic disorders, lymphedema occurs in less than 20% of cases, but when present, causes significant morbidity. Other less common lymphatic abnormalities may include pulmonary, intestinal, or testicular lymphangiectasia, chylothorax or chylous ascites, hypoplasia of the inguinal and iliac lymphatic vessels, absent or atrophied thoracic duct, or localized lymphedema in the scrotum or vulva. [12,17]. Lymphatic involvement was absent in our patients.

Skin manifestations, NS patients may present with pigmented nevi (25%), cafe au lait spots (10%), keratosis

pilaris is common (in the upper arms), and in cases where it affects the face, the eyebrows may be absent [18] . The skin is hyperelastic, the hair thick and curly and the nails dystrophic.In our study, the skin of our patients was hyperelastic, our patient had curly and thick hair, but we noted the absence of cafe au lait spots and neavus.

Vision and hearing abnormalities, ocular anomalies are common (95%), strabismus (40% -65%), refractive errors (60%), amblyopia (33%) or nystagmus (10%). The anterior segments may be affected (60%), including cataracts. Other possible ocular abnormalities are optic nerve hypoplasia [19]; hearing loss secondary to otitis media is a frequent complication (15%-40%), sensorineural hearing loss is less frequent [20].Regarding our patients, nystagmus was noted in our patient, however, the visual and auditory evoked potentials returned normal in both patients.

Neurological manifestations, cognitive and behavioral changes, cognitive functioning is within the normal range in up to 80% of cases [21]. Other psychiatric disorders described in these patients include mood disorders, difficulties with communication and interpersonal interaction, and attention deficit hyperactivity disorder [10]. Language disorders are more common in children with NS than in the general population. In our patients, cognitive functioning was normal, which is consistent with the literature.

Up to 55% of cases have a mild to moderate tendency to bleed. Severe bleeding occurs in 3% of cases. Coagulation studies reveal prolonged bleeding times, deficiencies of factors VIII, XI and XII, thrombocytopenia and abnormalities of platelet function. These manifestations appear individually or in combination [18]. In our study, our patients did not present with a bleeding syndrome and the platelet count was normal, but platelet function and coagulation factors were not investigated.

Acute leukemia and myeloproliferative disorders (MPD) have been described in some patients. The 218C>T mutation in the PTPN11 gene is associated with a predisposition to MPD, which most often resolves spontaneously [19]. In rare cases, individuals with NS can develop a fatal MPD, typically juvenile myelomonocytic leukemia (JML). However, the prognosis of NS patients with JML is better than that of non-NS patients with JML. [18]

Despite advances in molecular testing, NS is diagnosed primarily on the basis of clinical features and an underlying genetic mutation is not identified in 20% to 30% of patients. Diagnostic criteria now universally accepted were first developed by Vander Burgt in 1994 and revised in 2007. (Figure 1)[18]

The differential diagnosis must include other RASopathies the most common being neurofibromatosis type 1, as well as other syndromes unrelated to the RAS-MAPK pathway, such as Aarskog syndrome, Turner syndrome, Baraitser-Winter syndrome, Williams syndrome, Peutz-Jeghers syndrome and King-Denborough syndrome.

Regarding the genetics of Noonan syndrome [3], RASopathies including NS are currently thought to result from deregulation of the RAS-MAPK pathway; To date, mutations in more than 20 genes have been described in association with NS with the greatest heterogeneity of known loci. Several genes currently known to be involved in NS PTPN11; SO * S1; RAF * 1; BRA * F; MAP * 2K1; KRA * S; NRA * S; RIT * 1; SHO * C2; PPP * 1CB; SO * S2 RR * AS; RAS * A2; SP * RY1; LZT * R1. In our study, our 2 patients benefited from a genetic study revealing a mutation of the PTPN 11 gene in the heterozygous state in one patient and absence of a

mutation characteristic of an NS in the 2nd patient, which is consistent with the data from the literature which shows that a genetic mutation is not identified in 20 to 30% of patients.

One option for the symptomatic treatment of NS is recombinant human growth hormone (rhGH). Its use for this indication was approved by the United States Food and Drug Administration in 2007, and more recently by the European Medicines Agency [3]. Studies in the literature have reported a significant increase by GH in the z-score of final height of 1.4 ± 0.8 (corresponding to 9.5 ± 5.4 cm) [25,26,27,28], although some studies have reported significantly smaller increases. Recent studies have found short-term improvement at higher doses[27] , although long-term safety and efficacy data are lacking; the decision to use rhGH in patients with NS must be made on a case-by-case basis[3] ; Factors to consider are height, age (early initiation is preferable to maximize prepubertal linear growth), presence of comorbidities (hypertrophic cardiomyopathy is not a contraindication but requires close cardiological monitoring), genotype (in patients with variants associated with a high risk of cancer, the use of rhGH should be considered with great caution and, if initiated, requires close monitoring). The recommended initial dose is 33 µg / kg / day (to be increased to 66 µg / kg / day if poor response). If the patient has a poor response despite 1 to 2 years of high-dose therapy, consider discontinuing therapy, as maximal response should occur in the first few years of treatment. Our patients have not benefited from growth hormone therapy due to lack of resources.

Regarding treatment prospects, strategies to decrease activity in the RAS-MAPK pathway have attracted considerable attention, with preclinical trials showing favorable results. Off-label use of trametinib in 2 patients with severe hypertrophic cardiomyopathy in NS who are on the transplant waiting list was successful in resolving myocardial involvement almost completely. [29] It has also been hypothesized that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (called statins) may be useful by inhibiting RAS farnesylation and its localization to the plasma membrane. An animal model of statin use in NS found increased growth by improving chondrocyte differentiation [15], and a phase 3 clinical trial is currently underway to evaluate the efficacy of statins in improving growth in NS.

Prenatal diagnosis of Noonan syndrome is possible thanks to antenatal ultrasound which shows nuchal translucency in the first trimester, hydramnios (1/3 of cases), pleural or pericardial effusions and antenatal manifestations of cardiac and renal malformations. The very non-specific nature of the antenatal signs, the complexity of the SN at the molecular level; explain why prenatal diagnosis is rarely considered in the absence of a family history. [2]

Regarding prognosis and quality of life, long-term data are scarce. One study found that one-third of adults with NS attended school as children with learning disabilities,. and 20% attended mainstream school while receiving academic support. Forty-three percent of the study participants had achieved school certification. Reported data on health-related quality of life showed no difference from the general population [22]. Adults with NS require long-term cardiological follow-up. An absence of symptoms, normal cardiac output, and Pulmonary artery pressure and right ventricular pressure less than 100 mmHg are associated with a good prognosis [23]. Mortality associated with hypertrophic cardiomyopathy is the same in patients with NS and patients without NS. The mortality was 9% at a mean age of 60 years [24]. In our

study, after 2.5 years, the evolution of our patients is good with a normal echocardiography.

Regular follow-up by a cardiologist is essential until adulthood, the frequency of which dépends on the anomalies observed. It is essential to follow the psychomotor development of young children, to detect a possible deafness, and to orientate as soon as possible the children presenting difficulties towards a rehabilitation structure. In the case of language disorders, sustained speech therapy can be very beneficial. Hearing and vision tests are recommended. Regular evaluation of growth parameters is performed until the end of adolescence. Genetic counseling on the risk of transmitting the disease to his descendants is recommended when the patient is old enough to have children.

Conclusion

The Noonan syndrome is a genetic pathology with a very rich clinical symptomatology whose treatment requires a multidisciplinary collaboration (pediatrician, ophthalmologist, pediatric surgeon). The prognosis is conditioned by the involvement of vital organs, essentially the heart. This syndrome is a source of visual impairment, possibly due to ocular damage.

Table 1: diagnostic criteria for noonan syndrome 2007

Feature	A = Major	B = Minor
1 Facial	Typical face dysmorphology	Suggestive face dysmorphology
2 Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defect
3 Height	<P3*	<P10*
4 Chest wall	Pectus carinatum/excavatum	Broad thorax
5 Family history	First degree relative with definite NS	First degree relative with suggestive NS
6 Other	Mental retardation, cryptorchidism and lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

HOCM: hypertrophic obstructive cardiomyopathy;

*P3 and P10 refer to percentile lines for height according to age, with the normal range of variation defined as P3-P97 inclusive

Definitive NS: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs

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