Novel insights in Noonan syndrome

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Abstract
Noonan syndrome is an inherited developmental disorder, classically identified by typical appearance, short stature, and cardiologic impairment. Nowadays it is recognized as part of RASopathies, i.e. a group of genetic disorders affecting the RAS-MAPK pathway. Diagnosis and clinical management of Noonan syndrome are challenging for the general paediatrician and children require thorough multidisciplinary assessments throughout growth. Particularly, they must be referred to both paediatric endocrinologists and paediatric cardiologists. Prompt diagnosis is possible and genetic counselling for affected families is essential. This paper reviews clinical features and current treatment guidelines of Noonan syndrome in order to allow general paediatricians to better care children and adolescents with Noonan syndrome and to ensure a proper multidisciplinary approach.

Introduction
Noonan syndrome (MIM 163950) (NS) is a genetic developmental disorder, historically identified by typical physical appearance associated to short stature and congenital heart defects. Jaqueline Noonan, a paediatric cardiologist, was the first to characterize the syndrome: she identified nine children with remarkably similar faces, short stature, significant chest deformities and pulmonary stenosis. Initially, NS was mixed up with Turner syndrome; the fact that males could be affected and reports of normal karyotypes helped to separate these two entities. In 1994, Noonan syndrome was mapped to 12q24.1 and genetic heterogeneity was documented. In 2001 Tartaglia and colleagues identified the first gene (PTPN11) associated to NS [1]. To date, pathogenetic mutations have been demonstrated in several genes across RAS-MAPK signal transduction pathway (mitogen-activated protein kinase), that is an important regulator of cell growth, differentiation and senescence [2]. Gradually, other syndromes related to NS have been described: NS with multiple lentigo or LEOPARD syndrome (MIM 151100), Noonan-like syndrome with loose anagen hair (MIM 607721), Costello syndrome (MIM 218040), cardio-facio-cutaneous syndrome (MIM 115150), type 1 neurofibromatosis (MIM 162200), and Legius syndrome (MIM 611431) [2,3]. Currently, NS and related disorders are collectively named RASopathies, i.e. a group of diseases related by constitutional dysregulation of the RAS signalling pathway and phenotype resembling NS [3]. Cardiac involvement, impaired growth, intellectual disabilities, predisposition to cancer and ectodermal, muscle and skeletal defects are variably represented. An extensive description of all RASopathies goes beyond the intent of this paper: we will provide a general overview of NS as a paradigm for this group of pathologies. In fact, the aim of this paper is to summarize the general characteristics of NS with special attention to cardiac disease and GH therapy; people with NS and other RASopathies require prompt diagnosis and multidisciplinary interventions at different stages of their lives.

Epidemiology
With a cumulative incidence of about 1 per 1000 live births, RASopathies represent one of the largest groups of developmental disorders [2]. The incidence of NS is estimated to be 1 case per 2500 live births [1,4]. It is the most common cause of congenital heart disease after trisomy 21.

Pathogenesis
NS is a genetic pathology due to sporadic or inherited mutations, with normal karyotype; most cases are transmitted in an autosomal dominant manner and for these reasons males and females are equally affected. As similar autosomal dominant disorders, a significant percentage of cases result from de novo mutations. NS is characterized by incomplete penetrance: parents can be affected by mild forms. In addition, it seems that the mother is more often the transmitting parent: it depends on normal pubertal development in affected females, while affected males usually present cryptorchidism [5]. As mentioned, pathogenetic mutations are part of RAS MAPK signal transduction pathway. In addition to PTPN11, that accounts for approximately 50% of mutations, pathogenetic mutations have been demonstrated in SOS1, RAF1, KRAS, NRAS, SHOC2, CBL, BRAF, SOS2, RRAS, RASA2, SPRY1, LZTR1, MAP2K8, MYST4, and A2ML1 [2]. PTPN11, SOS1, RAF1 and RIT1 cover 93% of reported mutations. However, in 20-30% of all patients with NS, genetic mutations have not been identified [6]. PTPN11 (protein tyrosine phosphatase non-receptor type 11) gene encodes for SHP-2, a tyrosine phosphatase, that is involved in several developmental processes such as limb development, semilunar valvulogenesis, haemo poetic cell differentiation and mesodermal patterning and is widely expressed in several tissues such as heart, muscles and brain [7]. PTPN11 mutations result in a gain of function of SHP-2. There are no phenotypic features exclusive to a specific genotype, anyway genotype-phenotype correlations may be useful since there are significant differences in the risk of various NS manifestations based on the causative gene (Table 1). For instance, NS type 1 (MIM 163950), due to PTPN11 mutations, is characterized

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by frequent pulmonary stenosis and atrial septal abnormality, shorter stature, lower insulin growth factor-1 (IGF1) levels, more bleeding tendency, and feeding difficulties. In addition, some children may have feeding difficulties, justifying enteral nutrition in one-fifth of infants. This period of failure to thrive is self-limited [9]. Postnatal growth failure may appear from the first year of life. The mean height follows the lower limit of the normal population (third percentile or -2 standard deviation score SDS) until the age of puberty, after which it declines further as a result of delayed puberty and attenuated pubertal growth spurts. Since bone maturity is usually delayed, prolonged growth into the 20s is possible. Anyway, the final adult height is around -2SDS in both sexes; it is estimated 161-167 cm in males and 150-155 cm in females [13]. Specific growth charts are available and should be used in growth assessment of these patients [12]. To date, the primary cause of short stature in NS is unclear. For instance, insulin like growth factor 1 (IGF-1) concentrations are as low or low-normal in patients with PTPN11 mutations [14-16]. Anyway, the role of growth hormone in these children is still under study and is being disputed.

Neuropsychological development

Early developmental milestones may be delayed in NS infants, partly due to joint hyperextensibility and hypotonia, frequently described in these children. First words average age is around 15 months; this delay may be related to articulation deficiency, that is relatively common, hearing loss, or perceptual motor disabilities. During school-age about 50% of children present coordination disorders [17,18]. Individuals with NS have mildly lowered intellectual abilities, with IQ scores below 70 in 6%-23% of patients. Around a quarter of children affected by NS have learning disabilities and some of them require special education [17]. Attention and executive functioning seem to be impaired and autism spectrum disorders are more prevalent than in the general population [19].

Cardiac abnormalities

The prevalence of cardiovascular disease in Noonan syndrome is about 80-90% [9,12]. The spectrum of cardiac anomalies is wide, including pulmonary valve stenosis (PVS) and hypertrophic cardiomyopathy, atrial septal defect (ASD), atrioventricular canal defect (AVCVD), mitral valve anomalies, aortic coarctation, tetralogy of Fallot, ventricular septal defect (VSD) and aortic root dilatation. Atypical electrocardiographic patterns are present in approximately 50% of patients [20-22]. PYS represents 60-70% of cardiovascular disease in Noonan syndrome, HCM accounts for 20-30%, while ASD (10-30%), AVCVD (5-15%), VSD (5-10%) are less common. Vascular anomalies, including mainly aortic dissection, aortic root dilatation, or aneurysm of sinuses of Valsalva, can be found in patients with NS [21,22]. Cardiovascular defects have some specific features.

Pulmonary valve stenosis

Pulmonary valve stenosis (PVS) is characterized by a dysplastic pulmonary valve with fibrous thickening of the annulus and the leaflets and could be associated with a ‘supra-annular’ stenosis, due to fusion of the pulmonary valve with fibrous thickening of the annulus and the leaflets

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Clinical presentation

NS is a clinically heterogeneous disorder with multiple congenital malformations; it includes dysmorphic facial features, short stature, congenital heart diseases and parenchymal abnormalities and comorbidities. The diagnosis of NS is historically based on clinical findings using the scoring system by van der Burg (1997). Anyway, the distinctive phenotypic triad is made up by facial features, short stature and cardiopaties [9,10].

Physical appearance

Facial and musculoskeletal features most often lead to the diagnosis of Noonan syndrome. The facial appearance is most characteristic in infancy and early-to-middle childhood and becomes subtle in adulthood [9]. Newborns present tall forehead, hypertelorism with down-slaning palpebral fissures, low-set, posteriorly rotated ears with a thickened helix, a deeply grooved philtrum with high, wide peaks to the vermilion border of the upper lip and a short neck with excess nuchal skin and low posterior hairline. They have a triangular shape face. Infants have prominent eyes, with horizontal palpebral fissures, hypertelorism and full or ptotic upper eyelids; nose has a depressed root, wide base and bulbous tip. In childhood, facial appearance is often lacking in affect or expression. By adolescence, facial shape is an inverted triangle, wide at the forehead and tapering to a pointed chin. Eyes are less prominent and features are sharper; the neck lengths, accentuating skin webbing or prominence of the trapezius muscle. In the older adult, nasolabial folds are prominent, and the skin appears transparent and wrinkled [8-11]. Skin abnormalities are common: follicular keratosis over extensor surfaces and face is characteristic of NS spectrum, also café au lait spots and lentigo are more frequent than in the general population [8]. A characteristic pectus deformity and naevi, lentigo, and café au lait spots are typical [2,8].
of the valvular cusps with the wall of the pulmonary artery [20,21]. Intervention for this defect can then be surgical valvuloplasty, outflow tract patching or valve replacement; almost half of the individuals with NS need cardiac intervention. ASD, usually of the ‘ostium secundum’ type, is often in association with PVS. AVCD is generally partial and may be associated with subaortic stenosis or prolapse [22].

**Hypertrophic cardiomyopathy**

Besides asymmetrical septal thickening or concentric hypertrophy and decreased compliance of left ventricle, hypertrophic cardiomyopathy (HCM) presents higher prevalence of reduced diastolic function and LV outflow tract obstruction than in non-syndromic patients. In addition, the onset of hypertrophic cardiomyopathy is earlier (median age 6 months) [12]. Myocardial ischemia due to reduced myocardial perfusion through the increased myocardial mass is common among patients with HCM, including young adolescents with RASopathies. Coronary arteries abnormalities (dilation of main left coronary artery, anterior descending artery or right coronary arteries) contribute to explain the higher risk of myocardial ischemia in these patients; other frequent manifestations of HCM in RASopathies are arrhythmias. Supraventricular and ventricular ectopic beats are common and non-sustained ventricular tachycardia is frequent and related to the risk for sudden cardiac death [21,23]. It must be noted that survival of patient affected by NS and HCM 15 years after diagnosis is lower (71%) compared with those with NS without HCM (97%), supporting the hypothesis that HCM in Noonan syndrome is an important risk factor for death. Significant diastolic dysfunction and associated cardiac alterations have been advocated as the main cause [1,22]. Cardiac involvement in NS is related to genotype–phenotype correlation: PVS is more common (approximately 70%) in subjects with PTPN11 and SOS1 mutations, and it is less common (approximately 20%) in patients with RAF1 lesions. HCM prevalence is relatively low in patients with PTPN11 or SOS1 mutations, but it is overrepresented in RAF1-associated Noonan syndrome (approximately 75%). In patients carrying heterozygous RIT1 mutations, compared with the general NS population, the prevalence and severity of both HCM and CHD is higher [24].

**Genitourinary involvement**

About 10% of children with NS present renal abnormalities, the most common of which is dilatation of the renal pelvis. Less common abnormalities are duplex collecting systems, minor rotational abnormalities, distal ureteric stenosis, renal hypoplasia, unilateral renal agenesis, unilateral renal ectopia and bilateral cysts with scarring are reported less commonly [8,9]. Delayed pubertal development is usually observed both in males and in females. Cryptorchidism is noted in 60% to 80% of males and subsequently deficient spermatogenesis may be associated; on the other hand, female patients present normal fertility. For this reason, the affected parent who transmits the disorder is predominantly the mother [25].

**Ocular and acoustic involvement**

About 95% of patients present some kind of ocular abnormalities. In addition to external ocular abnormalities (e.g. hypertelorism and eyelid anomalies), NS patients may be affected by strabismus, myopia, astigmatism, amblyopia, and/or limited ocular motility. Approximately 55% of patients have an abnormal ophthalmological test [26,27]. In NS hearing loss due to otitis media is a frequent complication; progressive high-frequency sensorineural hearing loss is also described. Even for avoiding speech delay, it is recommended to provide hearing assessment at diagnosis of NS [28,29].

**Lymphatic abnormalities**

Lymphatic anomalies are typical of NS. Dorsal limb lymphedema, localized on the top of the foot and back of the hand, is common. Intestinal, pulmonary, or testicular lymphatic vessels could be altered: there are reports of chylous effusions of the pleural space and/or peritoneum and localized lymphedema of the scrotum or vulva [30]. Moreover, it is important to note that prenatal features suggestive of NS are often of a lymphatic nature.

**Bleeding diathesis**

NS can be associated with an increased risk of bleeding and bruising, caused by a variety of bleeding abnormalities. Factor XI is the most frequently lacking, followed by factor XII and factor VIII, with some patients presenting multiple-factor deficiencies; widespread thrombocytopenia and platelet aggregation abnormalities were also reported [31,32]. Early studies showed that the prevalence of coagulation defects in NS was even 30%, but several studies have highlighted that there is no strict correlation between coagulation study results and bleeding risk. In fact, NS patients with coagulopathy may show severe surgical haemorrhage as well as laboratory abnormalities with no clinical consequences. Anyway, since these patients undergo multiple surgeries (for example for cardiologic defects), it is important to regularly assess their bleeding risk [31-33].

**Risk of malignancies**

Predisposition to malignancy is an important concern in the prospective care of patients with RASopathies. In fact, the dysregulation of the RAS/MAPK signalling pathway typical of RASopathies is reported in the development of up to 20% of all sporadic hematologic and solid malignancies. Germline mutations appear to cause enhanced signalling activity although in a less robust way than in corresponding somatic mutations in genes underlying tumour formation. It is hypothesized that robustly activating somatic gene mutations causing cancer are not seen in germline RASopathies since they may cause embryonal lethality [34,35]. Both hematopoietic malignancies and malignant solid tumors were reported in association with NS. In a cohort of 632 individuals with molecularly confirmed NS, a childhood cancer standardized incidence ratio of 8.1 was described [34]. Among haematopoietic malignancies, the ones quite frequently reported include different types of leukaemia and lymphoma (Hodgkin’s and Non-Hodgkin’s types). Leukaemia is the most common malignancy associated with NS, germline PTPN11 mutation is described in most of cases. Specific mutations of PTPN11 or KRAS are associated with a myeloproliferative disorder (NS/MPD) resembling juvenile myelomonocytic leukaemia (JMML). NS/MPD occurs in neonates and infants, starts as a polyclonal disease and typically resolves over time. However, aggressive and monoclonal leukaemia that may be lethal have been reported [34,35]. Regarding malignant solid tumours, there are case reports of rhabdomyosarcomas, neuroblastomas, central nervous system tumours, testicular seminomas [36,37]. Costello syndrome is quite different than other RASopathies: it is characterized by solid tumour development in childhood and adolescence, but it is not associated with hematologic malignancies. Costello syndrome presents higher cancer risk than other RASopathies, especially for embryonal rhabdomyosarcoma, neuroblastomas, and early-onset bladder cancer. The cumulative incidence of cancer is 15% by age 20 years [35].

**Diagnosis**

NS is suspected clinically by observation of key features. Diagnostic criteria were developed by van der Burgt (2007): diagnosis is clinically
Table 2. Diagnostic Criteria of Noonan Syndrome by van der Burg [38].

| Features                  | A: Major                                      | B: Minor                                      |
|---------------------------|-----------------------------------------------|-----------------------------------------------|
| 1: Facial                 | Typical face                                  | Suggestive face                               |
| 2: Cardiac                | Pulmonary valve stenosis and/or hypertrophic cardiomyopathy | Other cardiac defects                         |
| 3: Growth                 | <3rd centile                                  | <10th centile                                 |
| 4: Chest wall             | Pectus excavates/carinatum                    | Broad thorax                                  |
| 5: Family history         | 1st degree relative affected by NS            | 1st degree suggestive of NS                    |
| 6: Other                  | Mild developmental delay, cryptorchidism, AND lymphatic dysplasia | Mild developmental delay, cryptorchidism, OR lymphatic dysplasia |

defined with Criterion 1A + one of 2A-6A/two of 2B-6B or Criterion 1B + two of 2A-6A/three of 2B-6B (Table 2) [38].

The diagnosis of NS is established by molecular genetic test. Usually it is performed using a multigene panel that includes pathogenic genes; in order to distinguish NS from cardio-facial-cutaneous syndrome and Costello syndrome, most available panels include the genes for these diagnoses, too. Alternatively, serial single-gene testing (SGT) may be considered: SGT starting with PTPN11 would be the next best first test. Different serial single-gene testing can be chosen evaluating the individual phenotype. In 30% of cases, indeed, the responsible gene remains unknown. Anyway, the suitability and sequence of gene testing should be decided by a clinical geneticist. Prenatal testing is possible if the NS-related pathogenic variants have been identified in an affected family member. On the other hand, when a child is diagnosed with the syndrome the diagnosis of NS should be considered in parents [12,39].

Prenatal characteristics

Cystic hygroma, skin oedema or nuchal translucency, pleural effusion and hydrops fetalis are frequently associated with NS in the prenatal period (50% of cases). These lymphatic system abnormalities were initially noted more than 20 years ago [40]. Polyhydramnios (73%) is common and is associated with decreased foetal swallowing. Renal alterations, such as pelviccasts, hydrenephrosis and increased kidney size, may be reported by prenatal ultrasound in about 20% of pregnancies [41]. It is difficult to identify cardiac involvement, including valvular dysplasia and hypertrophic cardiomyopathy: cardiac anomalies are diagnosed by foetal echocardiogram in 21% cases, while they are recognized in neonatal period in 80% of patients [18,41,42]. Anyway, these findings are nonspecific and may have different degrees of severity during pregnancy and among patients; therefore, the identification of prenatal echocardiographic abnormalities, particularly those of lymphatic system, requires not only karyotyping, but also targeted organ screening, in order to distinguish NS from other congenital disease (e.g. other RASopathies) [42].

Management

In every child with NS, multidisciplinary evaluations are recommended in order to establish the extent of disease. Monitoring of anomalies found in any system is a paediatrician’s responsibility. In 2010 Dyscerne, a European consortium, developed management guidelines for different age groups. They suggest that every infant with NS must be referred to dietary assessment, full cardiac evaluation and renal echographic evaluation; they also consider measures of weight, height and occipital circumference at birth and monthly in order to investigate short stature. At the diagnosis, they recommend visual screening and to provide hearing assessment in the 2nd half of first year. Concerning neuropsychological development and neurological involvement, patients should receive a developmental assessment in the 2nd half of first year [6,39]. During childhood, cardiac evaluation is necessary to rule out the onset of HCM: echocardiogram is carried out annually until the age of three and then at 5 and 10 years old and follow up is carried on in elderly ages, if no anomalies are shown. Concerning growth, using NS growth charts in childhood is critical: children with a height below the mean for NS should be referred to a paediatric endocrinologist. Moreover, during early childhood talipes should be screened and later scoliosis must be monitored. Coagulation system must be screened at least once during childhood and before any major surgery. It is necessary to carry on visual screening. In order to prevent speech development problems, hearing should be monitored once a year. At primary and secondary school entry neuropsychological assessment must be evaluated as well as intellectual/cognitive abilities; learning difficulties could be a result of motor delay, executive dysfunctions and inattention. Speech therapy, learning support and physiotherapy are fundamental tools. During adolescence, cardiac, neurological and skeletal follow-up must continue as well as specific attention to coagulation disorders and lymphoedema. Delayed puberty should be carefully evaluated. Moreover, patients should be referred for genetic counselling, mutation testing and discussion of risks to children as well as options in pregnancy at an appropriate time [6,39]. The multitude of haematologic and solid malignancies reported in association with the RASopathies requires special clinical awareness for malignancy screening. Patients with these disorders should be evaluated for the presence of specific types of tumors reported with higher frequency in this population (such as leukaeemia, lymphoma, neuroblastoma, rhabdomyosarcoma, brain tumours, and bladder carcinoma) depending on clinical symptoms, examination, and laboratory findings. The lack of large cohort studies estimating the prevalence of tumors in these patients has complicated the establishment of specific screening protocols in those disorders, anyway recommendations for cancer surveillance in individuals with RASopathies have been published [35]. Since patients with RASopathies have mildly increased cancer risk, increased awareness and prompt assessment are necessary, while routine cancer surveillance is considered excessive in most cases. In patients with NS due to specific PTPN11 or KRAS mutations known to be associated with MPD/JMML, 3 to 6 monthly physical exams with spleen size assessment and complete blood counts with differential should be considered starting at birth (or diagnosis) and continuing until the age of 5 years [35].

Treatment

There is no single treatment for NS, but it is possible to treat many aspects of the condition. Treatment of different manifestations in NS is standard: it does not differ from treatment in the general population, even for cardiologic management. On this issue, it is important to remind that patients undergoing percutaneous balloon pulmonary valvuloplasty have a high re-intervention rate (65%) for residual valvar pulmonary stenosis. As regards HCM in NS, medical therapy (beta-blockers, disopyramide or calcium channel blockers (L-type) is the usual initial treatment, while a determining factor for considering invasive treatment occurs with a 50mmHg or greater gradient trough the LV outflow tract. Other factors to consider include the presence of subaortic stenosis (accessory fibrous connective tissue), abnormal insertion off the mitral valve, anomalous papillary muscles, mitral leaflet length anomaly, and mitral chordal attachments, all of which may be present in Noonan syndrome patients. Taking these factors into consideration, surgical myectomy can be utilized in Noonan syndrome with symptomatic HCM of an obstructive nature [23].

Anyway, the most concerning and debated aspect in NS treatment is growth hormone therapy. Recombinant human growth hormone
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rhGH is widely used for the treatment of short stature across several disorders, primarily with the aim of improving linear growth toward the normal adult range. The causes of short stature in NS are multifactorial and not completely clarified. Growth hormone deficiency, GH insensitivity, and neurosecretory dysfunction have been investigated in these patients [43-46]. rhGH (Norditropin) is licensed in the USA, Switzerland, South Korea, Israel, Brazil and the Philippines for the treatment of children with short stature due to Noonan syndrome, at doses of up to 0.066 mg/kg/day, whereas GH is not approved for this indication in Europe [43-47]. Some studies were performed to evaluate the effects of rhGH treatment in NS. For example, a Korean group enrolled 15 prepubertal NS children who received rhGH (50-75 microg/kg/day for 6 days a week for 3 years) and analysed pre and post treatment height, weight, bone age, IGFBP3 levels. They found increased height standard deviation score and serum IGFBP1 levels in all patients, while they noted a decreased response to rhGH in patients with PTPN11 mutations [48]. Furthermore, a Japanese randomized double-blind multicenter trial evaluated the effects of rhGH therapy in children with NS. Prepubertal children were treated with rhGH at two different doses 0.033 mg/kg/day and 0.066 mg/kg/day for 104 weeks; this study reported an increased height standard deviation scores and IGFBP1 levels for both doses, with greater improvement in patients who received the higher dose. No significant changes in glucose profiles and electrocardiogram or echocardiography findings were described [49]. rhGH treatment was evaluated by a Turkish group, registering IGFBP1 levels for both doses, with greater improvement in patients who received the higher dose. Even if short and long-term studies have demonstrated the effectiveness of rhGH therapy in NS, traditionally there is concern about rhGH effects on cardiac involvement and tumoral progression. Some studies reported no significant adverse events of rhGH therapy regarding progression of hypertrophic cardiomyopathy, alteration of metabolism and tumour development [51-53]. Several studies showed that blood glucose levels remain within normal ranges during rhGH therapy. As regards to cardiac involvement, there was no evidence of increasing ventricular wall thickness: a prospective rhGH trials of over 3 years showed that no children with NS experienced any serious complication of heart based on echocardiography [13]. Data on rhGH and tumour risk give no cause for concern, but small patient numbers and few documented cases prevent risk assessment [54]. Currently, there are two non-interventional multicentre studies assessing the effectiveness and safety of somatropin (Norditropin, particularly): the NordiNet International Outcome Study (NordiNet IOS; NCT00960128) and the American NordiNet Studies: Web-Enabled Research Program (ANSWER; NCT01009905).

Conclusions

NS represents the paradigm of RASopathies, e.g. a heterogeneous group of genetically transmitted disorders of RAS-MAPK signalling pathway. Historical identification was based on the triad typical face, short stature and cardiac involvement. Nowadays, specific phenotype and molecular bases of disease are well recognized; in fact, several pathogenetic gene mutations have been discovered. Prompt diagnosis is made possible by the knowledge of clinical features and it is confirmed by genetic tests. Moreover, a proper awareness of NS should prompt general paediatricians and paediatric endocrinologists to care affected children throughout their growth. Usually, the main concerns about treatment relate cardiac surgery and outcome and safety of rhGH therapy. To date, cardiac approach is the same of general population, even if overall outcome in NS is worse when several cardiac abnormalities are present. As regards to rhGH safety, several studies showed no progression of cardiac involvement and metabolic disturbances or even increased tumoral incidence. Up until today, hormone replacement therapy is approved in US, but not in Europe, though this may change in the future and influence daily management of NS patients by the general paediatricians.

Authorship

GD and FC contributed equally to writing the manuscript.

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