UPDATE ARTICLE
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Noonan's syndrome and related disorders: clinical-molecular update and guidelines

Sindrome di Noonan e sindromi correlate: caratteristiche clinico-molecolari e linee guida

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Summary

Noonan's syndrome (NS), LEOPARD syndrome (LS) and Noonan's-like/multiple giant cell lesion syndrome (NL/MGCLS) are clinically and genetically related conditions. The phenotype of these disorders is mainly characterised by short stature, facial dysmorphims, and congenital heart defects, in particular pulmonary valve stenosis and hypertrophic cardiomyopathy. In addition, individuals with LS present cafè-au-lait spots and multiple lentigines, while NL/MGCLS patients show giant cell lesions of bones, joints and/or soft tissues. These disorders are often due to missense mutations of the *PTPN11* gene, encoding for SHP2, a protein tyrosine phosphatase involved in RAS signalling. Here we propose clinical and molecular guidelines for baseline and follow-up management of affected individuals, with the aim of advising clinicians and scientists involved in the management of patients with NS and related disorders.

Riassunto

La sindrome di Noonan (NS), la sindrome LEOPARD (LS), e la sindrome simil-Noonan con lesioni multiple giganto-cellulari (NL/MGCLS), sono condizioni clinicamente e geneticamente correlate. Il fenotipo delle tre sindromi è principalmente caratterizzato da bassa statura, dismorfismi facciali e cardiopatie congenite, in particolare stenosi della valvola polmonare e cardiomiopatia ipertrofica. I soggetti con LS presentano anche macchie caffèlatte e lentigginosi, mentre quelli affetti da NL/MGCLS mostrano caratteristiche lesioni giganto-cellulari a livello delle ossa, articolazioni e/o tessuti molli. Queste condizioni sono spesso causate da mutazioni missenso del gene PTPN11, codificante per la proteina SHP2, una tirosina fosfatasi coinvolta nelle vie di trasduzione mediate da RAS. In questo articolo, vengono proposte delle linee guida cliniche e molecolari per la diagnosi e la cura dei soggetti affetti da queste condizioni, al fine di consigliare e guidare i clinici e i ricercatori coinvolti nella cura di pazienti affetti dalla NS e sindromi correlate.

Key words

Noonan's syndrome • LEOPARD syndrome • *PTPN11* • Guidelines

Parole chiave

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Introduction

Noonan's syndrome (NS), LEOPARD syndrome (LS) and Noonan's-like/multiple giant cell lesion syndrome (NL/MGCLS) are clinically and genetically related disorders. Based on clinical features, these conditions have been considered separate entities. The identification of *PTPN11* as a major disease gene underlying these disorders proves that NS and LS are allelic conditions, while MGCLS is an uncommon trait shared both by NS and LS. Individuals with these disorders present some characteristics more often than the general population (GP). This clinical and molecular update based on the available literature and on personal experience, aims to provide medical guidelines for the management of individuals with NS and related disorders,

along with suggestions for clinical diagnosis and follow-up for the management of these disorders.

Diagnostic features

Noonan's Syndrome

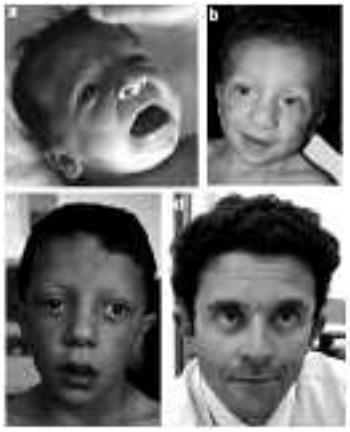
The term "Noonan's syndrome" was introduced by John Opitz in 1965, based on Jacqueline Noonan's report of 9 patients presenting with a Turner's-like phenotype and pulmonary valve stenosis (PVS) [1 2]. This condition had been described previously as "male Turner's syndrome" or "Bonnevie-Ullrich's syndrome" [3 4].

The prevalence of NS has been estimated in about 1 every 1,000-2,500 live-births, with a median age at diagnosis of 9 years [5 6]. NS is a mendelian trait with autosomal dominant inheritance, complete penetrance and variable expression. The facial appearance is characteristic, although consistently changing with age, being more striking at birth and in first infancy [7]. In general, the newborn shows a high forehead, with hypertelorism and downslanting palpebral fissures (95%), posteriorly rotated ears with a thick helix (90%), prominent philtrum (95%), thick lips, short neck with redundant skin on the back, and low-set posterior hairline (55%) [8] (Fig. 1). In the first infancy, a relative macrocephaly is present with prominent eyes, thick and ptosic eyelids, depressed nasal root with a large base and a bulbous tip. During childhood, the face lacks expression and appears myopathic, while during adolescence the facial shape is triangular, and the neck is webbed. Adults normally present prominent naso-labial folds and wrinkled skin.

A congenital heart defect (CHD) is detected in more than 80% of NS patients [9 10]. The most characteristic defect is PVS with dysplastic leaflets (40%) [10]. A partial form of atrioventricular canal defect, sometimes associated with subaortic stenosis, occurs in about 15% of these patients. Hyperthrophic cardiomyopathy (HCM), mainly involving the left ventricle, with onset in the first or second infancy, is found in less then 10% of the patients. Other CHDs include atrial septal defects, mitral valve anomalies, aortic coarctation, and, in rare instances, tetralogy of Fallot and ventricular septal defect (VSD).

The clinical diagnosis of NS is also based on other cardinal features, including short stature (below the 3rd centile), skeletal anomalies (pectus and spine deformities and cubitus valgus), lymphatic dysplasias, genitourinary anomalies, cryptorchidism, coagulation anomalies, and mild psychomotor delay [8 11]. NS patients can also manifest ocular anomalies, such as refractive errors and strabismus, together with asymmetric eye shape and size, and characteristic pale-blue iris [12]. Skin anomalies and asymptomatic hepatosplenomegaly are common [7 13]. Neurological anomalies, sensorineural deafness, myeloproliferative disorders and acute leukaemias are rare [8 14 15]. Diagnostic criteria and scoring systems have been outlined by Duncan et al. [16] and van der Burgt et al. [17]. However, no consensus has been reached so far, and the diagnosis of NS is clinical on the basis of its cardinal features [8].

Fig. 1. Noonan syndrome patients at different ages (a: 3 months; b: 3 years; c: 11 years; d: 38 years).



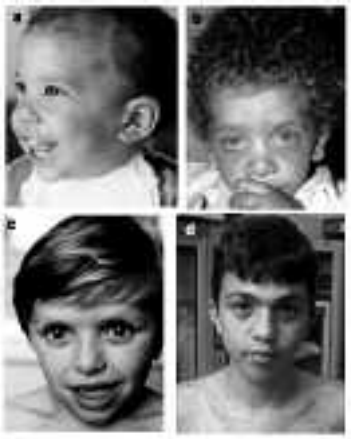
LEOPARD Syndrome

The acronym "LEOPARD" was suggested as a mnemonic of the major features of this disorder, including multiple lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, growth retardation, and sensorineural deafness [18 19]. This disorder is also recognized as Cardio-cutaneous syndrome, Moynahan's syndrome, Multiple Lentigines syndrome, and Progressive Cardiomyopathic Lentiginosis [20-22]. More than 200 cases have been described and one review has been published [22 23].

LS is a rare autosomal dominant multiple congenital anomaly syndrome, with high penetrance and markedly variable expression, displaying several clinical manifestations overlapping those of NS [23-25]. In the absence of a positive family history, differential diagnosis between these two conditions could be tricky, especially in the first years of life, when lentigines have not yet developed [25].

Facial dysmorphisms resemble those in NS, in particular ocular hypertelorism with palpebral ptosis and ear anomalies. However, facial anomalies are more often mildly expressed, compared to NS (Fig. 2); the neck is short, but not webbed [24]. Multiple lentigines (ML) are characteristic; they manifest as dispersed, flat, black-brown macules, mostly on the face, neck, and upper part of the trunk, sparing the mucosae. In general, lentigines appear at age 4-5 years, and increase to thousands until puberty. Café au lait spots (CLS) may also be present, alone or in association with ML, in about 70-80% of patients [24]. They precede the appearance of lentigines, being present since the first months of life. The most frequent CHDs are ECG anomalies and progressive conduction defects [22 26]. In 50-60% of patients, CHD overlaps those occurring in NS, although with a different incidence. HCM occurs in about 80% of LS with CHD; it can be congenital, but in general left ventricular hypertrophy becomes manifest during the second infancy, is progressive and paralleled by the appearance of ML (our

Fig. 2. LEOPARD syndrome patients at different ages (a: 10 months, b: 2 1/2 years, c: 6 years; d: 15 years).



unpublished data) [26]. Common clinical features include hypotonia, hyperelastic skin at birth, sensorineural deafness, either congenital or with a postnatal onset, bilateral cryptorchidism, hypospadia, and genital hypoplasia. Renal anomalies, such as horseshoe kidney, are rare [24]. Skeletal anomalies overlap those occurring in NS. Occasional psychomotor delay can be related to hypotonia, while mental retardation is rare [24].

Diagnostic criteria have been outlined by Voron in 1976 and include two or three distinct features at least, according to the presence or absence of ML [22]. However, clinical diagnosis is not always feasible, particularly in those sporadic cases of young patients without lentigines, in whom the phenotype overlaps that of NS or Neurofibromatosis-NS (NFNS). Congenital or early onset of distinct features, such as HCM, ML, sensorineural deafness, especially in association with hypotonia and CLS, are critical diagnostic clues for the diagnosis of LS in young patients [24].

Noonan's-like/Mulitple Giant Cell Lesion Syndrome

In 1974 Cohen et al. described a patient with short stature, moderate developmental delay, facial dysmorphisms, PVS, ML, pectus excavatum, cubitus valgus, hearing loss, multiple central giant cell lesions of bones, which were considered a new association, referred to as Noonan-like/multiple giant cell lesion syndrome (NL/MGCLS) [27 28]. This condition overlaps with both NS and LS. NL/MGCLS is characterised by giant cell lesions of bones, joints, and/or soft tissues, generalised hypomineralization, skeletal anomalies and delayed sexual development. However, the clinical phenotype is extremely variable, with complex and progressive clinical features [29].

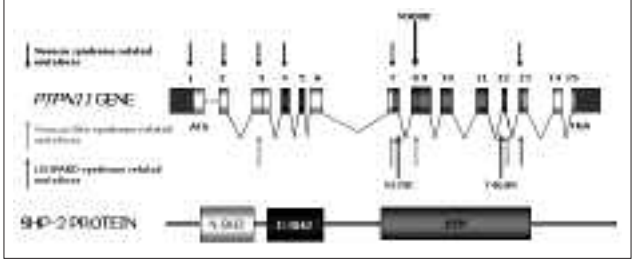
Underlying molecular defects

Genetic mapping studies in NS have shown linkage to chromosome 12q22-q24 (*NS1* locus) [30-32], and proved that this disorder is genetically heterogeneous [30]. In 2001, Tartaglia and coworkers identified missense mutations in the *PTPN11* gene as the causative event in NS patients linked to the *NS1* locus [33]. Accumulated data indicate that *PTPN11* is mutated in 40-50% of affected individuals, even though differences in inclusion criteria, recruiting strategies and relative abundance of sporadic and familial cases result in a variable mutation detection rate [34-36]. Subsequent studies have demonstrated that *PTPN11* gene mutations are a major cause of LS, occurring in about 90% of these patients, and also cause NL/MGCLS (50% of cases) [25 34 37-41] (Fig. 3). More recently, germline mutations in the KRAS gene have been documented in a small percentage of subjects exhibiting a severe phenotype at interface with cardio-facio-cutaneous syndrome (CFCS) or Costello syndrome [42 43]. A mutation in the *NF1* gene has been reported in a patient supposed to be affected by LS [44]. Conversely, screening of the *NF1* gene was negative in a cohort of *PTPN11* mutation-negative LS patients (our unpublished data).

The *PTPN11* gene encodes for the SRC homology 2 (SH2) domain-containing protein tyrosine phosphatase (PTP) SHP2, which is characterised by two amino-terminal, tandemly arranged SH2 (N-SH2 and C-SH2) domains and one catalytic (PTP) domain. This phosphatase acts as a cytoplasmic signalling transducer downstream of multiple receptors for growth factors, cytokines and hormones, and can modulate positively or negatively the signal flow, depending on the transduction pathway and the cellular context [45 46]. A knock-in mouse model for NS (*Ptpn11*^{D61G}) has been generated documenting early embryonic lethality of the homozygous *Ptpn11*$^{D61G/D61G}$ genotype, reduced viability of heterozygous embryos and features of NS, including cardiac defects, reduced length with preserved body proportions and facial dysmorphisms in the surviving heterozygotes [47].

Most *PTPN11* gene mutations are missense [48], and are prevalently spotted in exons 3, 8 and 13 among patients with NS, and in exons 7, 12 and 13 among patients with LS (Fig. 3). The mutations are unique in each condition, leading to specific genotype-phenotype correlations [34 35]. In particular, LS mutations correlate with the occurrence of HCM, while NS-causative mutations are frequently associated with PVS [34 35]. At present, missense *PTPN11* gene mutations have been detected in six out of 8 NL/MGCLS patients [24 34 40 49]. Remarkably, the same mutations have been documented also in NS and LS.

Fig. 3. Representation of the *PTPN11* gene coding sequence, SHP-2 protein and location of mutations. The most common amino acid substitutions are also indicated (longer arrows).



Modelling and biochemical studies indicate that NS-causing *PTPN11* mutations promote SHP-2 gain of function [34 48 50 51], while the recurrent LS-causing Y279C and T468M amino acid substitutions engender loss of SHP-2 catalytic activity [48 52].
A distinct class of somatic missense *PTPN11* gene mutations occur in myeloid and lymphoid malignancies [46 53]. These mutations differ from those found in NS, LS and NL/MGCLS [48]. Similarly to NS, biochemical and functional data suggest that somatic mutations contributing to leukemia promote SHP-2 gain-of-function [48 51 53-56], the mutated protein tyrosine phosphatase acting as an oncoprotein in cancer. Available data also support the idea that NS-causative mutations have less potency in promoting SHP-2 gain of function, compared to those occurring in leukaemia, while LS-related mutations result in a SHP2 loss-of-function.

Differential diagnosis

Differential diagnosis is mainly posed with CFCS and NFNS. CFCS is characterized by facial dysmorphisms, overlapping – although more severe than – those of NS, ectodermal anomalies, including keratosis pilaris, ulerythema ophryogenes, hyperkeratosis, sparse thin curly hair, sparse eyebrows and eyelashes, developmental delay, short stature, growth retardation, hypotonia, and CHD, in particular PVS and ventricular septal defects [57 58]. This condition is not related to *PTPN11* gene mutations [59 60], but is caused by mutations in genes encoding for proteins involved in the MAPK pathway (BRAF, MEK1 and MEK2), frequently mutated in cancer [42 61 62]. The NFNS clinical features include those of neurofibromatosis type 1 and NS-LS, and are largely caused by *NF1* gene mutations [63 64].

Clinical guidelines

These guidelines are based on the available literature and on personal observations of children and adults with NS, LS and NL/MGCLS. Due to the high frequency of NS and its features – notably overlapping those of LS and NL/MGCLS, we propose general recommendations, with some different clinical and therapeutic approaches for each, when available.

Baselines Studies

Regardless of the age at diagnosis, the following steps are recommended:

- a complete clinical examination, comprehensive of an auxological evaluation;
- a complete cardiological evaluation, comprehensive of clinical evaluation, blood pressure measurement at the four limbs, ECG with Holter, in case of arrhythmia, 2D-doppler-Echocardiogram and chest X-rays;
- genitourinary system evaluation with ultrasound and urinanalysis, in the presence of any anomaly;
- coagulation screening test, comprehensive of prothrombin and thromboplastin time, platelet counts and coagulation factors;
- multidisciplinary neuropsychological evaluation;
- neurological examination, with cerebral ultrasonography and/or MRI in the presence of macrocrania or if a cerebral malformation is suspected;
- ophthalmologic examination;
- hearing evaluation;
- genetic counselling and molecular analysis of the *PTPN11* and *KRAS* genes.

Follow-Up by System

Growth and nutrition

Birth length is usually normal, while weight is frequently over the 97th centile, due to neonatal oedema [8 24]. Nevertheless, patients frequently manifest poor sucking and recurrent vomiting, which could cause poor weight gain up to the age of 18 months [8]. After the first months, height is generally at the 3rd percentile until puberty, with reduced growth velocity and pubertal growth spurt [65]. Bone age can be delayed by age 2 years [6]. Pubertal delay may lead to prolonged growth potential into the 20s [6 66]. Normal adult height is present in 30% of NS individuals, while over half of the females and nearly 40% of males have an adult height below the 3rd percentile, independently of the presence of CHD, or the administration of growth hormones (GH) [67]. The biological basis of short stature is unknown, although some evidence suggests that patients with *PTPN11* gene mutations are exhibiting mild GH resistance and relatively poor response to GH treatment [68 69]. A few subjects shows GH deficiency. A number of studies have addressed the effect of GH therapy in NS patients [70 71], pointing to a positive effect on growth velocity, accompanied by an acceleration of bone age, thus supporting that GH accelerate the time when patients reach adult height. Growth monitoring should be ongoing for 6-12 months, using GP growth chart. In the presence of normal results, auxological parameters should be evaluated every 6 months. In case of growth deficiency, auxological parameters, bone age, nutritional status, and thyroid function must be assessed to rule out chronic diseases, along with complete blood chemistry, sedimentation rate, IGF-1, IGFBP-3, stimulated GH levels, and hypophyseal hormone analyses. When GH deficiency is detected, GH therapy is recommended only in the presence of proven GH deficiency. During hormonal treatment, growth must be assessed every 6 months, and bone age, complete blood chemistry and thyroid function evaluated every year. Also the cardiac status must be checked, in particular in the presence of HCM.

Cardiovascular system

When CHD is found associated with NS or LS, periodic assessment must be performed, as recommended by the cardiologist. Complete cardiologic evaluation, including ECG, Holter analysis, and effort stress test, are warranted every 2 years in individuals with NS, and, annually, in those with LS and NL/MGCLS, especially when ML be-

comes manifest. In general, mild PVS is associated with a good prognosis when stenosis is not progressive; in these cases, life-expectancies do overlap those in GP. In patients with severe PV dysplasia, outcome of the balloon valvuloplasty is not as good as in GP. According to the gradient between the right ventricle and pulmonary artery, a valvulotomy or a valvulectomy should be performed. HCM can be asymptomatic, and only sometimes worsens the prognosis, although it can reduce ventricular compliance. In case of a significant gradient between the left ventricle and the aorta, treatment with beta-blockers or calcium channel blockers is indicated. In the absence of any improvement, surgical removal of the left ventricular outflow obstruction is indicated. Conduction defects develop quite often in the second infancy and the cardiologist should indicate the proper follow-up and treatments. Subacute bacterial endocarditis profilaxis must be considered.

Genitourinary system

Renal anomalies, such as dilatation of the renal pelvis, renal hypoplasia, duplex systems, minor rotation anomalies, distal uretheric stenosis, unilateral renal agenesia, renal ectopy and renal cysts are common in NS and are usually not severe [8 72]. However, based on diagnosis, serial evaluations and urological follow-up, with periodic urinalysis, are recommended in the presence of genitourinary anomalies, with antibiotic treatment in case of infections, and, when indicated, surgical correction. Cryptorchidism is detected in 60-80% of males, and must be treated with hGC hormone replacement, or surgically, before age 2 years, if the testis does not reach its scrotal position. Male pubertal development and fertility may be normal, delayed or inadequate [13 66], and spermatogenesis defects are likely to be related to cryptorchidism. The majority of females is fertile. The pituitary-gonadal axis function must be evaluated before puberty, to assess the need for hormonal replacement treatment.

Lymphatic system

Lymphatic anomalies can be detected prenatally, and usually resolve during childhood [8 73]. Cystic hygroma is a quite common prenatal indicator of lymphatic dysfunction, and can be associated with scalp oedema, polyhydramnios, pleural and pericardial effusions and/or frank hydrops [74]. In the presence of a normal karyotye, CHD and other defects should be investigated. In postnatal life, dorsal limb lymphedema can be observed. In the case of marked lymphoedema, investigations by the specialist are indicated. Less common anomalies include intestinal, pulmonary and testicular lymphangiectasias, and chylous effusions of the pleural space and the peritoneum, which should be assessed and treated by the specialist [75-77]. Lymphatic anomalies can lead to complication after surgical interventions.

Skeletal system

The majority of NS patients present with chest abnormalities, most commonly pectus carinatum superiorly and excavatum inferiorly, teletelia, and rounded shoulders [8]. Additional features are cubitus valgus (50%), hyper-extensible joints, and clino-brachydactyly (30%). Scoliosis occurs in about 15% of patients, and, less frequently, kyphosis, spina bifida, vertebral and rib anomalies, and genu valgum. About 10-15% of individuals also manifest talipes equino-varus; joint contractures have been reported in 4%. Accordingly, annual assessment by the specialist must be performed, with radiological investigations, if required. In case of scoliosis, bracing or surgery may be indicated.
Malocclusion and ogival palate are often found. NL/MG-CLS patients present giant cell lesions in the mandible and, at times, in the extramandibular structures. Orthodontic evaluation must be performed in the first infancy, with orthodontic intervention in the case of malocclusion.

Haemathologic evaluation

Many NS individuals manifest coagulation defects, resulting in easy bruising or abnormal bleeding during surgery; at times these defects are asymptomatic and are detected only during laboratory testing [78]. However, these anomalies can increase intra- and postoperative risks. Adequate coagulation screening must be performed in the presence of prolonged bleeding or increased bruising, and before surgical interventions, providing haemostatic support if required; aspirin and aspirin-containing medications must be avoided.
The frequency of juvenile myelomonocytic leukemia (JMML) and acute lymphoblastic leukemia (ALL) is slightly increased in NS. JMML may regress without treatment or manifest with an aggressive clinical course or even evolve to acute myeloid leukaemia [14 15 79]. *PTPN11* mutation screening in patients with NS and JMML or ALL have disclosed distinct mutations usually not found in other patients, suggesting some genotype/phenotype correlation [53 80]. Accordingly, periodic haematological investigations must be performed in infancy and childhood in patients carrying NS/JMML with associated *PTPN11* mutations.

Developmental/Behavioural/Emotional aspects

Early developmental milestones may be delayed, likely in relation to hyperextensibility and hypotonia, occurring in about 50% of LS individuals [8 24]. In school, special teacher support is required only for 10-15% of these children. The IQ score falls within the normal range, with a mean full-scale IQ score of 84. However, from one quarter to one third of these individuals manifests learning problems that require special academic strategies [6 13 81]. Lower verbal performances can be related to hearing loss. In the case of developmental delay, specific assessment must be set up, including complete neuropsychological evaluation, and stimulation program should be initiated. When difficulties are encountered at school, formal psychological assessment must be performed to look for the presence of specific cognitive disabilities that could benefit from an alternate teaching method. Hypotonia can be treated and in general responds well to physical and occupational therapies.

Tab. I. Clinical and molecular assessment in patients with Noonan syndrome and related disorders.

Assessment	At diagnosis All conditions	During follow-up NS and NL/MGCLs	LS
Auxological			
Complete clinical examination	+	Every year	
Auxological evaluation	+	Every 6 months until puberty	
Bone age	Every year in the presence of growth delay Every 2 years in the presence of normal growth		
TSH, FT3, FT4, TPO			
IGF-1 and IGFBP-3			
Stimulated GH levels	In the presence of growth delay		
Hypophyseal hormones			
Cardiovascular system			
Complete cardiological evaluation (ECG, Holter analysis, Effort stress test)	+	in case of CHD at diagnosis: as recommended by the specialist if negative at diagnosis: Every 2 years	Every year
Echocardiogram	+	as recommended by the cardiologist	Every year and when multiple lentigines develop
Chest X-rays	+	as recommended by the cardiologist	
Genitourinary system			
Genitourinary evaluation	+	When indicated	
Renal ultrasound	+	When requested by the specialist	
Urine analysis	When requested by the specialist		
Lymphatic system			
Surgical evaluation	When requested by the specialist		
Skeletal system			
Othopedic evaluation	+	Annual assessment	
Spine Rx	If requested by the specialist		
Orthodontics			
Othodontic evaluation	From early childhood		
Haematological evaluation			
Complete blood analysis	+	Each year Every 6 months when a leukemia-associated PTPN11 mutation is detected	
Coagulation screening	+	In the presence of any sign or symptoms Before any surgical procedure	
Neuropsychological profile			
Neurological evaluation	+	Every year in childhood and infancy	
Psychological evaluation	+	Every year in childhood and infancy	
Logopedic evaluation	+	In the presence of language delay	
Cerebral ultrasound	In the presence of macrocrania		
EEG	In the presence of seizures		
Cerebral MRI	When indicated		
Ear, Nose and Throat			
ENT evaluation	+	When indicated	
Audiometric evaluation	+	Every year until puberty Then when requested by the specialist	Every year until adulthood
Skin			
Dermatological assessment	Referral to the specialist in the presence of skin problems		
Genetic evaluation			
Molecular analysis	+		
Parents/relatives genetic testing	If a mutation is detected in the affected individual		
Genetic counselling	+	Before reproduction	

Table II. Clinical and molecular assessments in patients with Noonan syndrome and related disorders

ASSESSMENT	AT DIAGNOSIS	DURING FOLLOW-UP	
	All conditions	NS and NL/MGCLs	LS
Auxological			
Complete clinical examination	+	Every year	
Auxological evaluation	+	Every 6 months until puberty	
Bone age	In the presence of growth delay every year In the presence of normal growth every 2 years		
TSH, FT3, FT4, TPO *IGF-1 and IGFBP-3* *Stimulated GH levels* *Hypophiseal hormones*	In presence of growth delay		
Cardiological			
Complete cardiological evaluation (ECG, Holter analysis, Effort stress test)	+	*in case of CHD at diagnosis:* as recommended by the specialist *if negative at diagnosis:* Every 2 years	Every year
Echocardiogram	+	as recommended by the cardiologist	Every year and when multiple lentigines develop
Thoracic X-rays	+	as recommended by the cardiologist	
Genitourinary			
Genitourinary evaluation	+	When indicated	
Renal ultrasound	+	When requested by the specialist	
Urine analysis	When requested by the specialist		
Lymphatic			
Surgical evaluation	When requested by the specialist		
Orthopedic			
Othopedic evaluation	+	Annual assessment	
Spine Rx	If requested by the specialist		
Orthodontic			
Othodontic evaluation	From early childhood		
Hematological			
Complete blood analysis	+	Each year Every 6 months when a leukemia-associated *PTPN11* mutation is detected	
Coagulation screening Before any surgical procedure	+	In the presence of any sign or symptoms	
Neuropsychological			
Neurological evaluation	+	Every year in childhood and infancy	
Pychological evaluation	+	Every year in childhood and infancy	
Logopedic evaluation	+	In the presence of language delay	
Cerebral ultrasonography	In the presence of macrocrania		
EEG	In the presence of seizures		
Cerebral MRI	When indicated		
Ear, Nose and Throat			
ENT evaluation	+	When indicated	
Audiometric evaluation	+	Every year until puberty Then when requested by the specialist	Every year until adulthood
Dermatological			
Dermatological assessment	Referral to the specialist in the presence of skin problems		
Genetic			
Molecular gene analysis	+		
Parents/relatives genetic testing	If a mutation has been detected in the affected individual		
Genetic counselling	+	Before reproduction	

Neurological involvement

Neurological anomalies detected at diagnosis need appropriate follow-up assessments by the specialist. Otherwise, neurological evaluation must be performed only in symptomatic patients. Cerebral malformations are rare [82,83]. Association with malignant hyperthermia or myopathy has been reported in a few patients, and warrants CK evaluation before anaesthesia, and dantrolene prophylaxis, when CK values are increased [84].

Vision/Hearing involvement

Strabismus, refractive errors, amblyopia, nystagmus and colobomas (mainly in LS individuals), may be present, requiring periodic assessment by a specialist [12]. Surgical treatment is indicated only in case of severe strabismus or ptosis.

Hypoacusia secondary to otitis media is found in about 1/3 of NS individuals, indicating appropriate antibiotic therapy and transtimpanic drainage**,** in the recurrent forms. Sensorineural deafness can be frequent (3% in NS, 18% in LS), and progressive in LS, recommending annual hearing assessment until puberty in NS, until adulthood in LS, and hearing aids, if needed [8,24].

Skin involvement

NS individuals frequently manifest scalp hair anomalies and keratosis pilaris (14%) involving the face, of congenital onset and progressing until puberty [8]. CLS may be found in NS, but are typical in LS, together with ML; in general they develop after the age of 4-5 years [24,25]. LS newborns also have hyperelastic skin [24]. Dermatological assessment should be performed by the specialist, when indicated; annual evaluations are recommended in the case of GH therapy. In the presence of ML or CLS, total UVA-UVB protection should be adopted.

Rare features

A few patients with NSRC develop autoimmune diseases [8], vascular anomalies, as Moyamoya disease [85] and cavernous hemangiomas [86], rhabdomyosarcomas [87] and congenital intrahepatic portosystemic venous shunt [88]. Follow-up and treatments should be indicated as for GP.

GENETIC COUNSELLING

Genetic counselling must be offered at diagnosis. NSRC are inherited as autosomal dominant traits, with complete penetrance and a highly variable clinical phenotype. Genetic heterogeneity has been demonstrated. De novo germline *PTPN11* mutations are preferentially paternal and are associated with advanced paternal age [89]; 30 to 75% of patients have a positive family history. In familial cases, maternal transmission is more frequent (mother/father ratio: 3:1), most likely because of reduced male fertility. Germinal mosaicism has not been reported so far; therefore recurrence risk is not increased after the birth of a sporadic case. However, accurate clinical assessment of asymptomatic parents is required, including evaluation of photographs taken during childhood, to exclude mild clinical features, in particular in the case of NS.

The diagnosis of NSRC is clinical. A negative molecular testing result does not rule out the diagnosis. After molecular analysis, critical re-evaluation of the index case is indicated for the early detection of characteristics related to the specific mutation. For example, careful investigations must be performed if a leukemia-related mutation is detected in the patient, including complete chemical blood analysis every 6 months during childhood.

Prenatal molecular diagnosis is available to parents carrying a definite mutation. In addition, prenatal diagnosis of a NSRC can be suspected by ultrasound in the presence of cystic hygroma or nuchal lucency in a chromosomally normal foetus. The detection of an associated CHD, in particular PVS or HCM, can be an additional clue to the diagnosis. Among foetuses with normal chromosomes, in 2% of cases, the diagnosis of NS is made in the first trimester by the evidence of nuchal oedema [90-92]. Since height and weight are usually normal in NS newborns, foetal growth parameters are not helpful in making the diagnosis.

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List of abbreviations

ALL: acute lymphoblastic leukemia; CFCS: cardio-facio-cutaneous syndrome; CHD: congenital heart defect; CLS: Café au lait spots; GH: growth hormones; GP: general population; HCM: Hyperthrophic cardiomyopathy; JMML: juvenile myelomonocytic leukemia; LS: LEOPARD syndrome; ML: Multiple lentigines; NFNS: Neurofibromatosis-NS; NL/MGCLS: Noonan's-like/multiple giant cell lesion syndrome; NS: Noonan's syndrome; PTP: protein tyrosine phosphatase; PVS: pulmonary valve stenosis; SH2: SRC homology 2 (SH2); VSD: ventricular septal defect.

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