CHAPTER 7

Developmental and Neurological Features of Noonan Syndrome

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Abstract

The neurological aspects, including cognitive and behavioral functioning, of the clinical manifestations of individuals with Noonan syndrome (NS) are extremely variable and poorly understood. Results of different studies have yielded variable data, but showed that a large proportion of the patients with NS were affected in different areas of the nervous system: central nervous system malformations, cerebrovascular abnormalities, developmental delays, speech disorders, early motor milestones delay, hypotonia and hypermobility of joints, recurrent seizures, ocular problems, hearing loss and neuromuscular (peripheral neuropathy). Although most individuals with NS have normal intelligence, about one third have a mild intellectual disability, some have learning difficulties and psychological and behavioral problems, such as stubbornness, irritability, and poor self-esteem. This variability is likely related to the patient's specific genetic mutation.

Keywords: Neurological manifestations, Developmental milestones, Cognition, Speech/language, Learning, Behavior, Psychological and mental health

Nomenclature

ADHD	Attention Deficit Hyperactivity Disorder
ASD	autism spectrum disorder
EEG	Electroencephalography
FS-IQ	full-scale intelligence quotient
GABA	gamma aminobutyric acid
GTPase	Guanosine Triphosphatase
IQ	intelligence quotient
MAPK – RAS	mitogen activated protein kinase signaling pathway
MAPK/ERK	mitogen activated protein kinase signaling cascade
MCHAT	Modified Checklist for Autism in Toddlers
MRI	magnetic resonance Imaging
NS	Noonan syndrome
WRAML-2	Wide Range Assessment of Memory and Learning, Second Edition

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INTRODUCTION

Noonan syndrome (NS) is an autosomal dominant multisystem disorder variably expressed. Affected individuals have distinctive facial features, short stature, cardiovascular defects, and other congenital anomalies [1]. The estimated prevalence of NS is between 1:1000 and 1:2500 live births [2]. Most physicians will treat patients with NS during their career. NS is caused by the dysregulation and/or mutations in genes in the RAS-mitogen activated protein kinase (MAPK) signaling pathway (Fig. 1). This pathway is essential in the regulation of the cell differentiation, growth, and senescence, all of

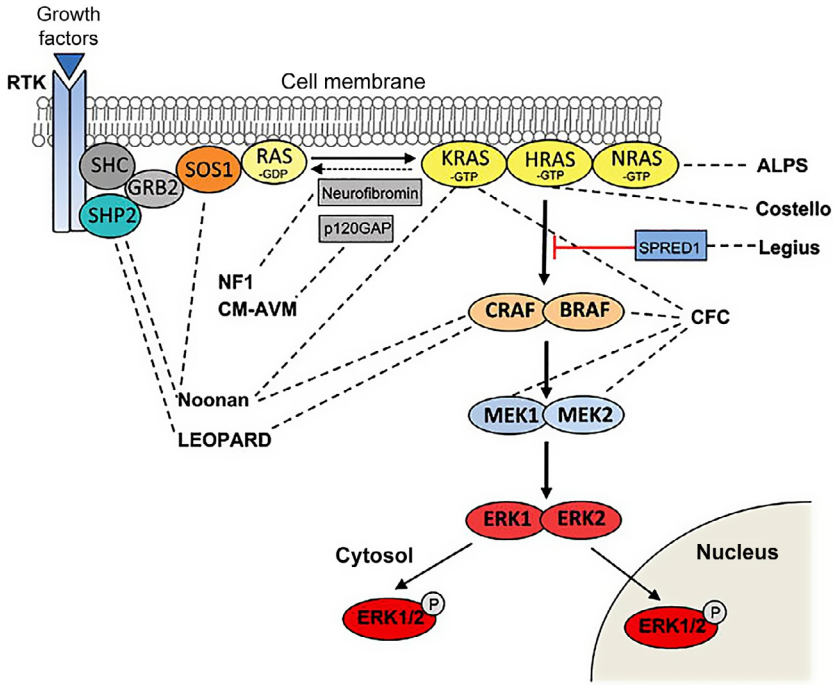

Fig. 1 The Ras/mitogen-activated protein kinase (MAPK) signaling pathway and associated developmental syndromes (indicated by *dashed lines*). The MAPK signaling pathway of protein kinases is critically involved in cell proliferation, differentiation, motility, apoptosis and senescence. The Ras/MAPK pathway proteins with germline mutations in their respective genes are associated with Noonan, LEOPARD, gingival fibromatosis 1, neurofibromatosis 1, capillary malformation-arteriovenous malformation, Costello, autoimmune lymphoproliferative (ALPS), cardio-facio-cutaneous and Legius syndromes. *(Permission pending Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev. 2009;19(3):230–6.)*

which are critical to normal development [3,4]. NS has high phenotypic variability and shares clinical features with other rare conditions from the group of so-called RASopathies. These include LEOPARD syndrome, craniofaciocutaneous syndrome, Costello syndrome, and Noonan-like syndrome with loose anagen hair [5]. Besides the common manifestations (cardiac disease, short stature, and facial anomalies), in certain patients, the syndrome has developmental and neurological implications.

Noonan syndrome was first described by pediatric cardiologist Dr. Jacqueline Noonan in 1963. Heterogenous clinical findings, including developmental and neurological conditions, were observed. Most patients have a normal intelligence quotient (IQ) but up to 35% may have mild intellectual disability. Some affected individuals may have abnormal delays of skills requiring the coordination of mental and muscular activity, learning disabilities, and language delays. These delays may manifest as hypotonia, difficulties in speaking, mild hearing loss. Inattention and challenges with executive functioning have also been reported. Many adults have relatively normal cognitive functioning except for lower information processing speed [6].

MOLECULAR PATHOGENESIS

Noonan syndrome is part of the group of so-called RASopathies, which are caused by mutations in the genes that encode for the ERK-MAP kinase signaling pathway. These mutations have profound effects on cellular development. The ERK-MAPK pathway is downstream from the fibroblast growth factor receptor. Disruption of the ERK-MAPK pathway during embryogenesis impedes neural crest cell development and causes defects in cardiac, craniofacial, and central nervous system structures [7].

The MAPK/ERK pathway (Ras-Raf-MEK-ERK pathway) consists of a series of intracellular proteins which facilitate the transmission of information from extracellular receptors to the nuclear DNA and other cytoplasmic effectors. This pathway regulates the activity of transcription factors. Cellular growth and differentiation are controlled by multiple extracellular signals, many of which activate this pathway (the Ras/mitogen-activated protein (MAP or ERK) kinase cascade). These extracellular signals, regulated by the kinase (ERK) subfamily of mitogen-activated protein (MAP) kinases, comprise the central elements of one of the most important and best-studied intracellular signaling pathways [8]. These receptors are physically and

functionally linked to the ERK cascade through a diverse group of molecular adapters that couple them to the activation of the GTPases of the Ras family. The MAPK/ERK signaling cascade plays an important/critical role in brain development, memory, learning, and cognition. Mutations in this pathway can cause developmental syndromes [7]. RAS proteins activated via phosphorylation events will activate the RAF-MEK-ERK cascade. The activated ERK enters the nucleus and will modulate transcription and activity of cytoplasmic targets. These effects will generate short-term and long-term cellular responses. All the genes implicated in NS code for proteins in this pathway. Abnormal Ras-ERK signaling has also been linked to some neuropsychiatric conditions, mental retardation syndromes, and drug addiction.

During development, the ERKs respond to growth factors through the activation of receptor tyrosine kinases. In the mature nervous system, ERK is part of the mechanism for synaptic plasticity in several different brain structures, and its activation is necessary for the long-term consolidation of memory [9].

During postnatal life the ERK-MAPK pathway is involved in synaptic function, especially in GABAergic neurons. Disruption of GABAergic projections, from the medium spiny neurons in the striatum, interrupts inhibition of excitatory glutamatergic and dopaminergic pathways, leading to cortical inhibitory-excitatory imbalances. Changes in GABAergic function in the hippocampus may affect memory and learning. Mutations or deletions in this signaling pathway generate these imbalances that may lead to developmental syndromes associated with impairment in cognitive functioning and autistic features [10].

The understanding of the role of the RAS-MAPK pathway in neurodevelopment is even more intricate because both loss-of-function and gain-of-function mutations are associated with RASopathies and have been shown to have differential effects on brain function in animal models [11].

DEVELOPMENTAL AND NEUROLOGICAL MANIFESTATIONS

Noonan syndrome is clinically heterogenous, and patients can have different developmental and neurological manifestations, such as early motor milestone delay, hypotonia and joint laxity/hypermobility, central nervous system malformations, learning difficulties, speech/language disorders and behavioral conditions (stubbornness, irritability, body image problems, and poor self-esteem).

BIRTH PARAMETERS

Prenatal features are nonspecific but include polyhydramnios, hydronephrosis, pleural effusion, edema, cardiac defects, distended jugular lymphatic sacs, cystic hygroma, and increased nuchal translucency [12,13]. During intrauterine life, some fetuses may show relative macrocephaly [14]. Birthweight and head circumference and body length at birth are usually normal [5], but approximately 40% of children fail to thrive in infancy [15,16]. According to a clinical study of NS, most patients had a normal head circumference at birth (the group mean was in the 50th percentile), even though the children were short and underweight. Some children had microcephaly or macrocephaly. Also, about 50% had a height less than the 3rd percentile, and 43% had the weight less than in the 3rd percentile [17].

DEVELOPMENTAL MILESTONES

Many children with NS have delays in their early motor development milestones. This may be related to hypotonia and joint hyperextensibility, and, during early childhood, it could be a result of the congenital heart disease, failure to thrive, and skeletal anomalies [1].

According to a study of 151 children with NS in the United Kingdom, 26% had delays in the mean age of motor milestones. The average age for sitting unsupported was around 10 months (SD 4.5 months), in the group of 126 patients for which this information was available. The age of independent walking was available for 112 cases and had a mean of 21 months (SD 10.2 months) [17].

Children with NS showed a higher rate of clumsiness and poor coordination. Seventy-one percent of NS children between 2 and 19 years, in a UK study of 27 NS children, showed clumsiness [18]. Another study showed that developmental coordination disorder was present in about 50% of school-age children. Gross motor skills were more impaired than fine motor skills, communication, and social skills [19]. Subsequent studies confirmed impaired manual dexterity, which was significantly correlated with verbal and nonverbal intellectual functioning on the Purdue Pegboard Test [20].

Children with NS have delay in their speech development. In the study of 151 children with NS, the age of speaking in simple two-word sentences was known for 102 children and occurred around 31 months (SD 9.6 months) [17]. In the same study, hearing tests were performed on 146 members of

the group, and hearing loss was reported in 58 children (40%). In a large majority, this was due to serous otitis media. Nerve deafness, requiring hearing aids, was detected in five children (3%) [17].

SPEECH AND LANGUAGE DEVELOPMENT

Speech and language pathology is common in children and adults with NS. A study of language phenotype showed that language impairments were more frequent than in the general population and were associated with higher risk for reading and spelling difficulties [21]. The average age when first words were spoken was around 15 months [21]; and simple two-word phrases emerged, on average, between 31 and 32 months [17]. In this study, the age of two-word phrases was known for 102 children, and this mean age was 31 months (SD of 9.6 months).

Feeding problems during infancy in NS patients were identified as a predictor of language development. The mean age for speaking two-word phrases was 26 months for those with no feeding difficulties and 39 months for those with feeding difficulties that required nasogastric feeding tubes [22]. The feeding problems present were described as poor suck, swallow, or gagging reflex, recurrent vomiting, food refusal, and intestinal dysmotility [23,24].

Language delay was found in 20% of patients with NS and may be related to mild hearing loss, perceptual motor disabilities, or articulation deficiencies. Articulation abnormalities were common (72%), but patients usually responded well to speech therapy [15]. In a study on 66 children and adolescents, language impairment was significantly correlated with nonverbal cognition, hearing, articulation, phonologic memory, and motor dexterity, but no specific aspect of language was selectively affected in these patients [25].

A study of language abilities and pragmatic skills focused on 17 patients with NS and an age and gender matched control group, found that 76.5% of the children in the NS group were identified with language impairments compared to 2 children (11.8%) in the typically developing group [26].

Problems with language development were found to be linked to subsequently delayed development of academic skills. Reading and spelling skills were strongly correlated with language ability and nonverbal cognitive ability in patients with NS [21]. This study also suggested that social aspects of language are also affected, particularly male participants, but more studies regarding social communication are needed.

OCULAR AND VISUAL FINDINGS

Patients with Noonan syndrome are affected by different anatomical ocular abnormalities, widely spaced eyes, down slanting palpebral fissures, ptosis, and ocular motility problems such as nystagmus, strabismus, and vision abnormalities (refractive errors and amblyopia) [27].

Vision abnormalities were found in 94% of patients with NS [17]. In this study of 145 individuals, vision was tested and found to be abnormal in 80 participants (55%). Of these, 52 patients underwent a full orthoptic and ophthalmological evaluation and strabismus and amblyopia were detected in 33 patients (63%) and 16 patients (31%), respectively. Refractive errors (myopia and hypermetropia) were found in 35 patients (67%). In this cohort, normal eye examinations were found in only three patients (6%). In another study, refractive errors were found in 39 of 69 patients (71%), 53% had myopia, 14% had hypermetropia, and 13% had astigmatism. No relationship was found between eye abnormality and genotype [22].

In a study which evaluated the visual function in 24 patients with NS, it was found that 83% had abnormal results in tests involving ocular movement, acuity, stereopsis. Visual motor integration skills were reported to be significantly impaired in 33%, and 48% had minor impairment when they were asked to copy a set of increasingly complex geometric shapes [28]. In another study, the same author found that children with NS performed worse on tests of form coherence (39% impaired) relative to motion coherence (11% impaired). The authors suggested that children with NS may have great difficulties with ventral stream processing ("what" pathway used for object recognition) compared with dorsal stream processing ("where" pathway used for spatial processing) [29].

A study in adults with NS showed that up to 95% were affected by visual conditions such as strabismus, refractive errors, amblyopia, or nystagmus. Two thirds of patients developed anterior chamber abnormalities including cataracts. Fundoscopic changes were reported in 20% of patients and included optic head drusen, optic disk hypoplasia, and colobomas [30]. In adults with NS, visual motor integration was found to be equivalent to that of adults in the typical group [31].

HEARING IMPAIRMENT

Hearing loss was reported in 40% of the NS patients [17]. This study reevaluated the same cohort of patients 12 years later, and showed that the majority

of patients reported normal hearing. Only four patients had hearing loss due to serous otitis media and had unilateral or asymmetric bilateral conductive deafness. A further three patients had sensorineural deafness. Only two patients had mixed conductive and sensorineural hearing loss. None of the patients had cranial imaging to investigate the underlying pathology. One patient with profound sensorineural deafness had a *PTPN11* mutation (A124G) [22].

Another study reported that approximately 10% of affected individuals have auditory deficits in the low frequency range caused by sensorineural hearing loss, and 25% have deficits in the high frequency range [32]. Inner ear structural abnormalities, including temporal bone abnormalities, were reported in these patients [33,34].

NEUROLOGICAL MANIFESTATIONS

Neurological abnormalities and manifestations are not prominent features of NS and are variably present in patients.

A clinical study on 151 subjects with NS, showed that some patients had manifestations in different areas of the nervous system: 94% had abnormal vision or ocular problems, 76% had feeding difficulties, 50% had hypotonia and hypermobility of joints, 40% had abnormal hearing, 13% had recurrent seizures, 3% had hearing loss, and 3% had peripheral neuropathy and an increased incidence of cognitive issues, learning disabilities, and brain abnormalities [17]. Another study reported that 84% of patients had some type of neurological problem [35].

The patients with NS have specific cranial-facial characteristics including triangular shaped face, low hairline, widely spaced eyes, ptosis, and low set ears, but research suggests that structural brain abnormalities are rare. Most frequently seen defects are type I Arnold-Chiari malformations and hydrocephalus [17]. Arnold-Chiari malformation was reported in 11 NS patients. The true incidence is not known and opinions are divided. Some suggest that the observed association may be coincidental [36–39]. Other reported structural abnormalities included: myelomeningocele (in a patient with recurring tethering of the cord), spina bifida occulta, subarachnoid hemorrhage from aneurysm, syringomyelia, optic nerve glioma, medulloblastoma, benign schwannomas or malignant schwannoma [40], and neuroblastoma [41,42]. Association of neurofibromatosis type 1 with NS was also reported [43,44]. Relative megalencephaly, moderately enlarged subarachnoid spaces, and small posterior

Table 1 Neurological features with specific gene mutations

Gene	Developmental	Neurological features
PTPN11	Cognitive impairments, except for N308D and N308S mutations	–
SOS1	Normal or high intelligence	–
RAF1	–	–
KRAS	Severe intellectual disability	–
NRAS	–	Somatic mutations—choroid plexus papilloma, meningioma
BRAF	–	Somatic Mutations—low-grade astrocytomas
RIT-1	–	–
CBL	Developmental delay	Microcephaly
SHOC2	–	Benign external hydrocephalus, cerebellar tonsillar ectopia, periventricular nodular heterotopia, dysplastic corpus callosum
PPP1CB	Global developmental delay, intellectual disability	Macrocephaly
SOS2	–	–
LZTR1	–	Multiple schwannomas
A2ML1	–	–

fossa were reported in a few children with SHOC2 gene mutation [45]. Yet, there is no data to link specific gene mutation to these brain abnormalities (Table 1).

Cerebrovascular anomalies reported were arteriovenous malformations, aneurysms, hypoplasia of the posterior vessels, and Moyamoya [38,46,47].

Neuromuscular abnormalities manifested as abnormal joint hyperextensibility in 75 of 151 patients (50% of cases). Hypotonia was also a common clinical finding. Serum creatine kinase was measured in a cohort of patients, and the concentrations were in the normal range for age and sex. In the same cohort, three adults and one child presented peripheral neuropathy, with distal weakness and altered sensation, in whom spinal cord compression was ruled out and the investigation did not reveal any cause for the neurological findings [17].

Recurrent seizures were reported in 20 of 151 patients (13%) with NS. Grand mal seizures accounted for 14 cases (9%), temporal lobe epilepsy for four cases (3%), and febrile convulsions for two cases (1%) [17]. In the follow

up study, in which some of the patients had dropped out, two subjects developed seizures during the follow-up interval, giving a prevalence of 11/112 (10%) in the follow-up sample. The mean age of onset was 11 years in a range of 3–19 years. *PTPN11* mutations were identified in two subjects with seizures [22].

Electroencephalographic (EEG) findings were reported for 28 patients with Noonan syndrome. Twenty (71.4%) of these patients showed EEG abnormalities. The main finding was a diffuse, slow background. They observed diffuse, slow background with focal changes or normal background with focal changes that did not have specific correlation with neurological findings except for a patient with epilepsy, whose EEGs revealed predominantly focal changes. Recurrent seizures were observed in only one patient who also had cortical dysplasia. On the neurological examination, 82% of these patients had various degrees of other neurological abnormalities including slow motor and mental development, spasticity and, in some cases, hypotonia. Their seizures responded well to antiepileptic medications. The researchers concluded that abnormal EEGs should be considered part of the NS [48].

INTELLECTUAL FUNCTIONING, MEMORY, AND ATTENTION

Several studies have shown that while most patients with NS have normal intelligence, the intellectual abilities of NS children are generally lower compared to typical children, and there is a higher risk for intellectual disability.

In a study by Cesarini et al., the IQ scores of NS patients ranged between 70 and 120 [49]. Within the group with normal intelligence, IQ was determined to be 10 points less compared to unaffected siblings or family members and one standard deviation below that of the general population. Most of these patients attended regular education, but between 10% and 40% required special education. According to the researchers, the heterogeneity of the cognitive abilities can be in part attributed to the individual affected genes or types of mutations [49].

It was shown that individuals with most *PTPN11* gene mutations and those without any known mutations more frequently had cognitive impairments than those with SOS1 mutations. However, the N308D and N308S substitution mutations in *PTPN11* were either associated with a mild or no cognitive delays. Whereas SOS1 positive NS individuals had verbal and nonverbal cognitive skills in the average range or higher. Other factors also

contributed to differences in cognitive functioning such as motor dexterity, hearing loss, and parental education. Severity of cardiac condition did not seem to play any a role in cognitive functioning [20].

Heterozygous mutations in the *PPP1CB* gene are associated with Noonan syndrome-like disorder with loose anagen hair. The *PPP1CB* gene is highly expressed in the brain throughout the developmental process. Along with other features of NS these mutations have been reported to include global developmental delay and intellectual disability as well [50].

In another study, the IQ scores of children with NS ranged between 64 and 127, with a median of 102. The authors showed that mild intellectual disability was seen in up to 35% of patients. The authors mentioned that the full-scale IQ may shield the possible presence of specific verbal or praxis disabilities [51]. IQ scores in the intellectual disability range (below 70) were reported in 6%–23% of patients with NS [52,53]. Studies on larger groups of young patients with NS did not find differences in intellectual functioning between boys and girls [20].

No significant difference was found between full-scale IQ in a group of adults with NS and community controls matched for age, gender, and education level [54]. About 75% of children with NS perform well in a regular classroom setting and 25% have learning disabilities [19], with 10%–15% of patients requiring special education [52]. Verbal IQ was found to be slightly lower compared to performance IQ [19,55]. Results from a study which administered tests of verbal, visual, and working memory from a standardized memory battery performed by WRAML-2 showed relative strength on verbal memory tasks when compared with visual memory and working memory tasks [56,57]. As with the FS-IQ, in adults with NS there were no significant deficits in delayed verbal recall or delayed visual recall. This finding suggested that memory problems may not be evident in adulthood. It is also possible that adults could be using compensatory strategies to overcome learning and memory deficits [31].

Patients with NS may have attention deficits and attention deficit hyperactivity disorder (ADHD) that may be linked to their academic difficulties. Attention deficits were reported in children with NS in a study by van der Burgt et al. [58]. Other earlier studies, based on parental reports, showed that children with NS have difficulties with attention and hyperactivity when compared to typical children [18,19,52].

A recent study showed that children with NS had higher rates of ADHD diagnosis (31%) than a group of unaffected siblings. According to this study, their attention skills were correlated with their intellectual performance.

This suggests that lower IQ is a risk factor for attention difficulties or that the symptoms of inattention interfere with their cognitive and learning abilities [53].

There was contradicting information regarding auditory and visual memory from two different studies. According to Pierpont et al., children with NS had weaker performance on auditory and visual working memory, with 34% showing significant impairment [57]. Another study reported that adults with NS did not show significant deficits on auditory working memory or other executive functioning tasks compared to the control group, except for self-reported higher rates of subjective executive functioning problems [31].

PSYCHOLOGICAL AND MENTAL HEALTH PROBLEMS

Attention and executive functioning is a common neuropsychological challenge for children with NS [53]. In a study of 32 children and adolescents with NS and their 16 typical siblings, children with NS had higher rates of ADHD and reduced performance compared with unaffected siblings on attention measures.

Adaptive behavior in children with NS is lower compared to age-matched typical children. Younger children had difficulties with motor skills and daily living skills, whereas older children had difficulties with social and communication skills. Researchers did not find differences in motor and daily living skills between boys and girls affected by NS. By school age and adolescence, NS patients showed that these discrepancies between the domains of adaptive functioning disappeared [21].

Social skills are another area where patients with NS have significant difficulties, especially by showing social immaturity and diminished interactions with other children [59,60]. The parents of children with NS also reported more attention seeking behavior compared to typical children that resulted in higher levels of stress in these parents [60].

Children with NS have poor muscle tone, which affects their athletic abilities and decreases their participation in sports, consequently, reducing their opportunities for socialization [5].

Based on checklists, such as the MCHAT (Modified Checklist for Autism in Toddlers), some studies reported an increased level of autism spectrum disorder (ASD) in 12% of children with NS [61]. When these children were evaluated clinically using DSM criteria, none of them met diagnostic criteria for ASD. In another study, 21% of participants with NS showed

elevated ASD symptoms, based on screening measures, compared with 0% in a group of their unaffected siblings [62]. Although 12%–21% of patients with NS were reported as having autistic features, most of them did not meet the full diagnostic criteria for ASD.

Adults with NS reported higher levels of difficulties with interpersonal interactions than unaffected adults [54]. Surveyed adults with NS reported that they experienced teasing or bullying as children because they had short stature or looked different compared to their peers [30,55]. As a result of these past experiences, patients with NS may show difficulties with psychological adjustment, depression, social anxiety, impairments of social skills, and academic problems [63]. No particular syndrome causing behavioral disability or psychopathology was observed in patients with NS, and self-esteem was comparable to age-related peers [19].

Reports from studies by Dr. Noonan showed that depression and anxiety may be frequently associated with NS as self-reported by affected adults. In a study of adults with NS [30], 49% reported being diagnosed and taking medications for anxiety and depression [64], but when they were tested using standardized evaluations, no significant differences in depression and anxiety were found between adults with NS and typical adults [54]. Although there are several case reports of patients with NS having different psychiatric disorders, including alcohol abuse, anorexia nervosa, bipolar disorder, panic disorder, obsessive compulsive disorder, and schizophrenia [30,59,65], there is no clear evidence to show that mental illness is more common in adults with NS.

Regarding quality of life based on self-reported questionnaires, no significant differences were found between adults with NS and the general population [55,66], except that NS patients had lower levels of education, graduation, and partnership and higher rates of mortality [55,66].

EVALUATION OF PATIENTS WITH NOONAN SYNDROME

Once a child has been diagnosed with NS, to establish the extent of neurological involvement and the needs of the individual, the following evaluations are recommended: complete physical and neurologic examination, growth parameter plotting on NS growth charts, ophthalmologic evaluation, hearing evaluation, brain and spine MRI if neurologic symptoms are present, multidisciplinary developmental evaluation, and consultation with a clinical geneticist and/or genetic counselor.

MANAGEMENT OF THE DEVELOPMENTAL AND NEUROLOGICAL MANIFESTATIONS OF NOONAN SYNDROME

Given the potential for developmental delays, once the extent of neurological and developmental involvement has been established in a NS patient, early intervention becomes very important to help patients reach their potential. Some patients may require multidisciplinary evaluation and care. Special services which would help affected children include: physical therapy, occupational therapy, speech therapy, special education, social skills, vocational services, and medical management of neurological problems.

Management guidelines were developed by American and European consortia, and the management is optimized to and presented as age-group specific guidelines that emphasize screening and testing for common health issues. There are three papers published with management guidelines/consensus statements: one developed in Europe at the University of Manchester, UK sponsored by DYSCERNE [67]; and two developed in the United States [5,24].

The guidelines are divided into recommendations for four age groups: Neonatal and Infancy (0–1 year old), Childhood (1–11 years old), Adolescence (11–18 years old), and Adulthood (18+ years old). By combining the recommendations from the three papers mentioned earlier, presented here are only those which apply to developmental, neurological, vision, and hearing problems.

I. Recommendations for the Management of Noonan Syndrome in Neonates and Infancy (0–1 year old)

In this group, screening is recommended in four areas:

Neuropsychological and behavioral issues: Infants need to be referred for formal developmental assessment during the second half of their first year. If they have delay caused by hypotonia, the patient is recommended management as per the general population. Hypotonia will improve with occupational and physical therapy.

Neurological involvement: Potential complications in infancy include seizures, craniosynostosis, hydrocephalus, and Arnold-Chiari malformation. A low threshold should be considered for investigation of suggestive neurological symptoms (abnormal eye movements, headache, and changes in head circumference) and for referral for brain/spine MRI, if needed.

Vision screening: Anterior or posterior segment ocular abnormalities have been described in NS. Once the diagnosis has been established, infants will need a referral to ophthalmology for baseline evaluation and follow up as deemed appropriate by the ophthalmologist.

Hearing assessment: Infants will need a referral for baseline evaluation during the second half of their first year. Hearing problems should be managed as per the general population.

II. Recommendations for the Management of Noonan Syndrome in Childhood (1–11 years old)

Neuropsychological and behavioral issues: Hypotonia and motor delay are common in NS but not necessarily followed by difficulties in adult life. Typically, these will improve with occupational and physical therapy. If the patient has hypermobility, he or she should be referred for occupational therapy.

Screening for developmental delay and speech delay and a full neuropsychological assessment should be done at entry into primary and secondary school, and if/when symptomatic. Management will be as per the general population.

Patients will need an assessment of cognitive abilities, executive function, and attention and learning difficulties. Some patients will need special education and ongoing support for learning and development.

Neurological management: As in the previous age group, a low threshold should be considered for investigation of neurological symptoms that are suggestive of seizures, hydrocephalus, and Arnold-Chiari malformation and for referral for brain/spine MRI, if needed.

Vision screening: Management is the same as for the previous age group. If any vision abnormality is suspected referral recommended, if not already under the care of an ophthalmologist.

Hearing assessment: Patients with NS have an increased risk for conductive hearing loss, but sensorineural hearing loss is rare. Hearing ability needs to be followed on a yearly basis in this age group to prevent speech problems.

III. Recommendations for the Management of Noonan Syndrome in Childhood (11–18 years old)

Neuropsychological and behavioral issues: If they have difficulties with daily living or social skills, patients in this age group will benefit from social skills training and programs that teach daily living skills.

Adolescents with NS may develop mood and anxiety disorders and may benefit from psychotherapy or pharmacological management.

Neurology: Individuals are at risk for the same neurological complications: seizures, craniosynostosis, hydrocephalus, and Arnold-Chiari malformation. There are no recommendations for routine screening. If symptomatic, individuals will need to be referred for brain/spine MRI and for management of epilepsy as per the standards for the general population.

Vision screening: Recommendations remain the same as for the other age groups. If individuals with NS are not already under ophthalmologic management, they should be referred to an ophthalmologist, if needed.

IV. Recommendations for the Management of Noonan Syndrome in Adulthood (18+ years old)

Neuropsychological and behavioral issues: In adults with NS, neuropsychological assessments may be needed if mood/anxiety problems or if intellectual impairment is suspected. Adult patients need attention and intervention for social skills, as this group is predisposed to social isolation as these patients are at risk of living without a partner. They will need access to support for employment, self-help, and independent living.

Neurology: Possible neurological conditions in adults with NS are the same as those for younger age groups. They will need referral for brain/spine MRI if suspicions for these problems arise. Management will be as per the general population.

Vision screening: Adults with NS can have the same eye and vision problems as at younger ages. If not yet under care, they should be referred to an ophthalmologist for evaluation, if needed.

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