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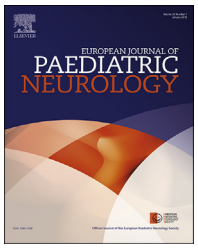

Original article

Psychopathological features in Noonan syndrome

Francesca Perrino [a,1], *Serena Licchelli* [b,1], *Giulia Serra* [b,f,g], *Giorgia Piccini* [b], *Cristina Caciolo* [b], *Patrizio Pasqualetti* [c,d], *Flavia Cirillo* [b], *Chiara Leoni* [a], *Maria Cristina Digilio* [e], *Giuseppe Zampino* [a], *Marco Tartaglia* [e], *Paolo Alfieri* [b,*], *Stefano Vicari* [b]

[a] *Center for Rare Diseases, Department of Pediatrics, Polo Salute Donna e Bambino, Fondazione Policlinico Universitario A. Gemelli, Catholic University, Rome, Italy*
[b] *Department of Neuroscience, Unit of Child Neuropsychiatry, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[c] *Service of Medical Statistics and Information Technology, Fatebenefratelli Foundation for Health Research and Education, Rome, Italy*
[d] *Language and Communication Across Modalities Laboratory (LaCAM), Institute of Cognitive Sciences and Technologies (ISTC-CNR), Italy*
[e] *Genetics and Rare Diseases Research Division, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[f] *NESMOS Department, Sant'Andrea Hospital, Sapienza University of Rome, Italy*
[g] *Department of Psychiatry, Harvard Medical School, Boston, MA, USA*

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ABSTRACT

Introduction: Noonan syndrome (NS) is an autosomal dominant disorder characterized by short stature, skeletal and haematological/lymphatic defects, distinctive facies, cryptorchidism, and a wide spectrum of congenital heart defects. Recurrent features also include variable cognitive deficits and behavioural problems. Recent research has been focused on the assessment of prevalence, age of onset and characterization of psychiatric features in this disorder. Herein, we evaluated the prevalence of attention deficit and hyperactivity disorder (ADHD), anxiety and depressive symptoms and syndromes in a cohort of individuals with clinical and molecular diagnosis of NS.

Methods: The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS PL) has been used for the assessment of psychiatric disorders according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Multidimensional Anxiety Scale for Children (MASC) and the Children's Depression Inventory (CDI) have been assessed for the evaluation of anxiety and depressive symptoms and syndromes, whereas Conners Teacher and Parent Rating Scales-long version (CRS-R) have been used to evaluate ADHD.

Abbreviations: ADHD, Attention Deficit and Hyperactivity Disorder; CDI, Children's Depression Inventory; CI, Confidence Interval; CRS-R, Conners Teacher and Parent Rating Scales-long version; DSM-IV-TR, Diagnostic and statistical manual of mental disorder 4th ed., text rev.; K-SADS PL, Schedule for Affective Disorders and Schizophrenia Present and Lifetime version; ID, intellectual disability; NS, Noonan syndrome; NS-ML, Noonan syndrome with multiple lentigines.

* *Corresponding author*. Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, Rome 00165, Italy.
E-mail address: paolo.alfieri@opbg.net (P. Alfieri).

[1] These authors contributed equally.

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Results: The study included 27 individuals (67% males) with an average age of 10.4 years (range 6–18 years) receiving molecular diagnosis of NS or a clinically related condition, evaluated and treated at the Neuropsychiatric Unit of Children's Hospital Bambino Gesù and at the Center for Rare Diseases of Fondazione Policlinico Universitario Agostino Gemelli, in Rome. Twenty individuals showed mutations in *PTPN11*, five in *SOS1* and two in *SHOC2*. The mean IQ was 94 (Standard Deviation = 17, min = 56, max = 130). Seventy percent of the individuals (n = 19; 95% Confidence Interval = 52–85%) showed ADHD features, with six individuals reaching DSM-IV-TR criteria for ADHD disorder, and thirteen showing subsyndromal traits. Symptoms or syndrome of anxiety were present in 37% of the cohort (n = 10; 95% Confidence Interval = 19–56%), with two individuals showing anxiety disorder and eight cases exhibiting subsyndromal traits.

Conclusion: Our results show individuals with NS do present a very high risk to develop psychiatric disorders or symptoms during paediatric age. Based on these findings, pre-school assessment of inattentive, hyperactivity/impulsivity and anxiety/depressive symptoms is recommended in order to plan a personalized treatment for psychological/psychiatric issues in affected individuals. Dedicated prospective studies are required to confirm the present data and better characterize the psychopathological profile in NS.

1. Introduction

The RAS/MAPK signalling pathway is an important signal transduction cascade activated in response of a large array of extracellular stimuli. It controls multiple cellular processes, including proliferation, differentiation, survival and metabolism.[1] Moreover, it acts in multiple developmental processes, playing a role in controlling learning and memory as well as regulating cognition and behaviour.[2–4] The deregulation of signal flow through this cascade has been linked to a family of clinically related developmental disorders known as RASopathies[5,6].

Noonan Syndrome (NS, OMIM 163950) is the most common and clinically variable entity among the RASopathies. It has been firstly described by Jacqueline Noonan, who reported on nine patients with pulmonary valve stenosis, short stature, hypertelorism, mild intellectual disability (ID), ptosis, skeletal malformations, and cryptorchidism.[7] Clinically, NS is characterized by postnatal growth failure, characteristic craniofacial dysmorphism, a wide spectrum of congenital heart disease, skeletal and hematological abnormalities.[8] The prevalence of NS is estimated between 1:1.000 and 1:2.500 live births, with an equal distribution between the two sexes. To date, alterations in twelve genes (i.e., *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *BRAF*, *SHOC2*, *MEK1*, *CBL*, *RIT1*, *SOS2*, *RRAS*, *LZTR1* and *PPP1CB*) have been identified causing NS or closely related condition, such as NS with multiple lentigines (NS-ML, OMIM 151100), Mazzanti syndrome, also known as Noonan syndrome-like disorder with loose anagen hair (NS-LAH, OMIM 607721) and the more recently described *CBL* mutation-associated syndrome (NSLL, OMIM 613563). In NS, psychomotor development may be delayed; in about 25% of affected individuals, neonatal hypotonia have been described, which usually improves along the time and ligamentous laxity is also present.

In a large fraction of subjects with NS, cognitive skills are generally within normal ranges, with an intelligence quotient (IQ) falling between 70 and 120.[9,10] Studies on cognitive abilities in individuals with a clinical diagnosis of NS suggest a prevalence of ID (IQ < 70) in approximately 20% of subjects,[9,11,12] with mild cognitive impairment in one-third of cases.[13,14] Nonetheless there are indications that up to 40–50% of NS patients require school accommodations.[15]

Moreover, difficulties in the "social cognition" have been described in patients with NS, in particular defects in emotion recognition leading to alexithymia (inability to express emotions verbally) in a significant proportion of cases.[16] Concerning the psychopathological aspects, mood disorders, social problems, communication difficulties, executive function impairment, and attention deficit and hyperactivity disorder (ADHD) have also been reported.[9–11,14,17–20] We recently investigated the behavioural profiles in RASopathies, and highlighted the presence of depressive and anxious symptoms, and social and attention problems in children with NS.[21] More recently, Pierpont et al. emphasized children with NS (1/3 of the study sample did not have molecular confirmation for NS) have higher rates of ADHD diagnosis (34% of cases), as well as reduced performance on behavioural attention measures compared with unaffected siblings.[22]

Increasing scientific interest has been focused on the relationships between genotype and cognitive/behavioural phenotype in genetic syndromes.[23] The presence of specific cognitive, psychiatric and behavioral profiles (including adaptive function impairment) has been well described for several syndromes and it has been considered to be independently correlated with the underlying genotype (also when controlled for environmental factors).[24]

The aim of the present study was to evaluate the presence and the prevalence of psychiatric symptoms and syndromes in NS and related disorders according to Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev; DSM-IV-

TR; American Psychiatric Association, 2000)[25] criteria in a sample of children and adolescents with clinical and molecular diagnosis of NS.

2. Materials and methods

Children affected by NS were recruited from the Child Neuropsychiatric Unit of the Children Hospital Bambino Gesù and the Center for Rare Diseases of Fondazione Policlinico Universitario Agostino Gemelli, Rome. Diagnosis of NS or a related RASopathy was made by experienced medical geneticists and paediatricians based on the clinical evaluation, and it was confirmed by molecular analysis. All but two mutations had previously been reported as disease-causing in patients with NS or a related trait. One sporadic subject exhibited a *SOS1* missense variant (p.Gln426Pro) affecting a residue located in a documented mutational hot spot of the gene.[26] A second case showed a *PTPN11* change (p.Arg186Trp) that had previously been reported as disease-causing in a single NS case.[27] In both families, parental DNAs were not available to demonstrate the *de novo* origin of the variant; consequently, both changes were formally considered as variants with uncertain significance. Participants were evaluated by an expert child psychiatrist and assessed with rating scales by experienced neuropsychologists. Parents gave their consent to perform the different type of tests.

General cognitive abilities were assessed with age-scaled tests based on age, language and cognitive skills including Raven Coloured Progressive Matrices Test,[28] Wechsler Preschool and Primary Scale of Intelligence (WIPPSI III),[29] Wechsler intelligence Scale for Children-Revised (WISC-III)[30] and Leiter International Performance Scale – Revised VR Battery, brief version (Leiter–R).[31] Intellectual abilities were classified according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association [APA], 2000).[25]

Children and parents have been interviewed using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime version (K-SADS PL),[32] to detect current and past features of psychopathological signs/psychiatric disorders in children and adolescents according to DSM-IV criteria (4th ed; DSM-IV; American Psychiatric Association [APA], 1994).[33]

Additionally, symptoms of anxiety and depression were respectively evaluated with the Multidimensional Anxiety Scale for Children (MASC)[34] and the Children's Depression Inventory (CDI).[35] The MASC is a 39-item self-report measure to assess physical symptoms, social anxiety, harm avoidance and separation anxiety. Children rated each item on a scale from 0 (never true about me) to 3 (often true about me). Total scores were reported on a standard scale, with a mean of 50 and standard deviation of 10. The CDI is a 27-item self-report inventory used to measure depressive symptoms in children and adolescents between the ages of 7–17. Each item is a set of statements from which the respondent has to select the response that best describes their thoughts and feelings in the past two weeks. A total score ranging from 0 to 54 is based on a five factors solution including mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. A score above 19 suggests the presence of clinically significant depressive symptoms.

Child behaviour was evaluated by using Conners Teacher and Parent Rating Scales-long version (CRS-R): the Conners Teacher Rating Scales-long version (CTRS-R:L)[36] and Conners Parent Rating Scales-long version (CPRS-R:L)[36]. The CPRS-R and CTRS-R report parent and teacher ratings of child behaviours involving problems in seven psychopathological areas: oppositional, inattention, hyperactive, anxious–shy, perfectionism, social problems, and psycho-somatic. Additionally, the items can be grouped into various indexes, including a global index, an ADHD index, and a DSM-IV-TR symptom index. Parents/teachers rated each item on a scale from 0 (not true at all) to 3 (very much true). Each subscale score is based on a standard scale, with a mean of 50 and standard deviation of 10. Significant results were considered from a low T-score of 61 (mildly atypical) to above 70 (markedly atypical).

2.1. *Procedures*

The Task Battery was administered to each participant individually and to her/his parents by an experienced psychologist during 2 sessions. Results of evaluation were classified in "presence of disorder", "traits of disorder", "absence of disorder". Participants with "presence of disorder" fulfilled all DSM IV-TR diagnostic criteria for ADHD or Anxiety disorders (Participants with an anxiety disorder had a DSM-IV TR diagnosis of General Anxiety, or Separation Anxiety, or Specific/Social Phobias).

Participants with "traits of disorder" showed a subsyndromal symptomatology (i.e. NOT fulfilling DSM-IV TR criteria for ADHD or anxiety disorders).

2.2. *Statistical analysis*

General Linear Models were used to compare groups. However, to compare the two cases with mutation in *SHOC2* to the other genotypes, single-case analysis was performed, following the procedure proposed by Crawford et al.[37]

Prevalence estimates were provided along with 95% Confidence Interval (CI) according to exact binomial approach. Concordance between raters (Parents, Teachers) was assessed by means of two-way Intra-Class-Correlation (ICC). SPSS 20.0 was used for the statistical analysis.

3. Results

The study included 27 subjects (18 males) with average age 10.4 years (range 6–18 years) with diagnosis of NS, NS-ML or NS-LAH. Twenty subjects were heterozygous for mutations in *PTPN11* gene, five carried mutations in *SOS1* gene and two carried a mutated *SHOC2* allele (Table 1).

The mean IQ was 94 (SD = 17, min = 56, max = 130). No differences in IQ were found between *PTPN11* and *SOS1* ($p = 0.212$). Since the group mutated in *SHOC2* gene was too small (2 cases) for standard inferential test, a single-case analysis was performed showing the subject's score of one subject (IQ = 56) was small enough to reject the null hypothesis he/she should be randomly drawn from *PTPN11* ($p = 0.014$) or *SOS1* ($p = 0.040$) population.

Table 1 – Descriptive characteristics of subjects with Noonan syndrome or a clinically related disorder.

Measure	All subjects	*PTPN11*	*SOS1*	*SHOC2*
Subjects (n)	27	20	5	2
Males (n, %)	18 (67%)	15 (75%)	1 (20%)	2 (100%)
Age (mean ± SD)	10.4 ± 3.3	10.6 ± 3.3	10.0 ± 3.6	13.5 ± 3.6
Range	6–18	6–18	6–15	11–16
(n) Mutations		(5) Asn308Asp (3) Asn308Ser (1) Asn58Lys (1) Phe285Ser (1) Thr468Met[a] (1) Ala72Gly (1) Ala72Ser (1) Arg186Trp[b] (1) Asp106Ala (1) Asp61Gly (1) Gly503Arg (1) Thr42Ala (1) Tyr62Asp (1) Tyr63Cys	(2) Arg552Lys (1) Gln426Pro[b] (1) Ile733Phe (1) Met269Thr	(2) Ser2Gly

[a] Clinical features of this subject fit NS-ML.
[b] This variant should be formally considered as a "variant of uncertain significance".

Table 2 – IQ and diagnosis of subjects with Noonan syndrome.

Measure	All subjects	*PTPN11* mutation	*SOS1* mutation	*SHOC2* mutation
Subjects (n)	27	20	5	2
IQ (mean ± SD)	94 ± 17	94.9 ± 13.8	104.4 ± 18.3	63.0 ± 9.9
Diagnosis (n, %)				
ADHD syndrome	6 (22%)	4 (20%)	1 (20%)	1 (50%)
ADHD traits	13 (48%)	9 (45%)	3 (60%)	1 (50%)
Anxiety syndrome	2 (7.4%)	2 (10%)	0 (00%)	0 (00%)
Anxiety traits	8 (29.6%)	4 (20%)	3 (60%)	1 (50%)

IQ intelligence quotient, ADHD attention deficit and hyperactivity disorder.

Whereas for the other subject with mutation in *SHOC2* gene (IQ = 70) the difference did not reach statistical significance ($p = 0.087$ vs. *PTPN11* and $p = 0.095$ vs. *SOS1*). Overall, these findings confirm previous studies documenting more relevant cognitive deficits in children harbouring mutation in *SHOC2* gene compared to *PTPN11* or *SOS1* genes.

Prevalence of ADHD and anxiety symptoms in study cohort are available in Table 2. One individual was affected by both disorders and four showed both ADHD and anxiety traits. Two of the six individuals with ADHD disorder showed ID (IQ = 56 and IQ = 62 within the *SHOC2* and *PTPN11* mutated subgroup, respectively). Only three patients did not present any trait or disorder.

The concordance between parents and teachers on Conners rating scale was low, ranging from ICC = 0.01 for the least concordant to ICC = 0.43 for the highest concordant item. RM-ANOVA with Item (13 levels) and Rater (2 levels) as within-subjects factor and Group as between-subjects factor indicated a significant Rater × Group interaction ($F(2,18) = 3.23$; $p = 0.0469$). As shown in Fig. 1 and confirmed by Bonferroni post-hoc analysis, when the raters were Parents, the only significant difference was between absence of ADHD and ADHD disorder ($p = 0.034$) with the group of ADHD traits in-between ($p = 0.184$ vs. absence; $p = 0.471$ vs. disorder). When the raters were Teachers, the group with ADHD disorder was characterized by values higher than both the others ($p = 0.027$ vs. absence; $p = 0.005$ vs. ADHD traits), while no difference was found between ADHD absence and traits groups ($p = 0.995$). These analyses suggest that parents tend to report high scores in ADHD traits already, while Teachers report these only in ADHD disorder.

Looking at each rater separately, no evidence of "Group X Item" interactions were found ($p > 0.3$ in both cases) while overall (across items) differences among groups were found (parents: $F(2,22) = 3.988$; $p = 0.033$; teachers: $F(2,19) = 7.183$; $p = 0.005$).

In our cohort, six subjects, all males, with a clinical diagnosis of ADHD, according to the DSM IV-TR criteria, showed clinically significant scores (above the cut off of 60) in all major subscales of CRS-R questionnaires filled by both parents and teachers (Table 3). In order to investigate the correlation between clinical diagnosis of ADHD and CRS-R subscale scores, a Spearman correlation was performed. We observed overall significant correlations, and specifically highly significant correlations in the subscales Total Clinical Global Impression (CGK, rho = 0.51, $p = 0.008$), DSM-IV-TR oriented for inattention subtype (CGL, rho = 0.54; $p = 0.005$) and DSM-IV-TR oriented for combined subtype (CGN, rho = 0.50; $p = 0.009$).

Only 2 subjects (both with mutation in *PTPN11*) presented an anxiety disorder, and other 8 cases showed anxiety traits; of the 2 patients suffering from an anxiety disorder one had ID and ADHD.

4. Discussion

To our knowledge this is the first study systematically assessing a wide spectrum of psychopathological features in

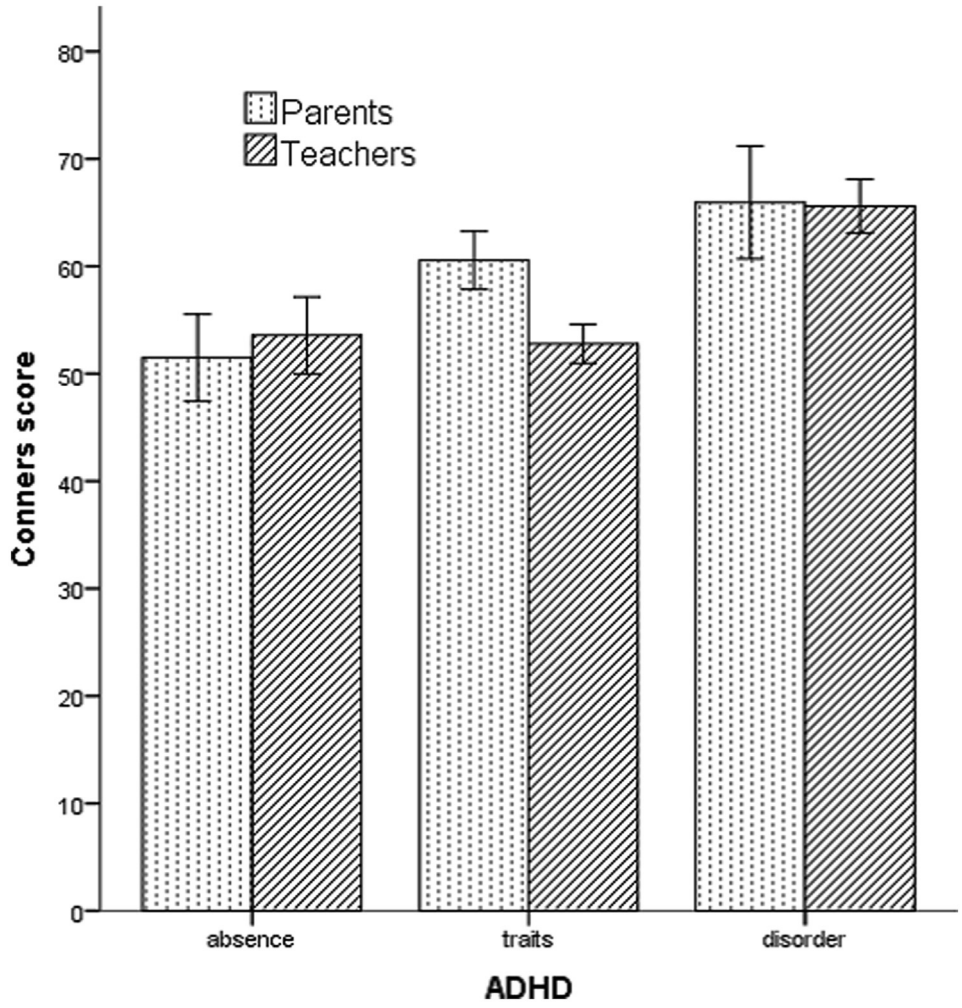

Fig. 1 – Scores obtained by Parents and Teachers on CPRS-R and CTRS-R.

children with a molecularly confirmed diagnosis of NS and clinically related disorders. Our data confirm the previously reported higher prevalence of ADHD in these disorders compared to the general population during juvenile age, but also for the first time report a considerably high prevalence of anxiety traits in children with NS and related conditions. The results of the present study also confirm the heterogeneity on IQ scores observed in patients with NS, which appears to be related to the genetic heterogeneity characterizing this disorder.

The characterization of the cognitive-behavioural phenotype associated to a genetic syndrome improves the

Table 3 – Conners scores subscales (pT) in subjects with ADHD.

Mutations of subjects with ADHD	ADHD Index		Clinical Global Impression		DSM-IV oriented for ADHD inattentive type		DSM IV oriented for ADHD hyperactive/ impulsive type		DSM IV oriented for ADHD combined type	
	Parents	Teachers	Parents	Teachers	Parents	Teachers	Parents	Teachers	Parents	Teachers
PTPN11 Asn308Ser	68	74	62	72	N.A.	59	75	70	74	66
PTPN11 Ala72Gly	74	78	75	72	70	71	79	81	77	80
PTPN11 Ala72Ser	64	63	56	61	78	74	59	57	69	67
PTPN11 Asp106Ala	77	59	80	68	76	71	81	47	82	61
SOS1 Met269Thr	87	N.A.	76	N.A.	86	N.A.	73	N.A.	83	N.A.
SHOC2 Ser2Gly	54	71	50	73	61	70	55	70	58	72

ADHD attention deficit and hyperactivity disorder, DSM IV diagnostic and statistical manual of mental disorder 4th ed.
N.A. not available.

knowledge on the specific condition by identifying the relationships between behavioural characteristics and underlying genotype, with a paramount impact on clinical practice.[23] Indeed, the identification of behavioural phenotypes has important implications for genetic counselling, diagnosis and management of children and families with genetic syndromes.

Seventy percent of subjects in our sample (n = 19; 95% CI = 52–85%) showed ADHD features, with six individuals (22% of the sample) meeting DSM-IV-TR criteria for ADHD disorder, and thirteen (48%) showing sub-syndromal traits. This finding confirms previous evidences of a greater prevalence of ADHD in NS compared to the general population in European countries,[22] and extends this result to our country showing a significant higher prevalence of ADHD syndrome in NS compared to the Italian juvenile population (22% in NS *versus* 3% in general population).[38] Moreover, the 48% prevalence of ADHD sub-syndromal traits appear to be 7-times greater in NS and related disorders compared to the 6.9% of reported prevalence in the Italian general population.[39] General estimated frequency (22%) of ADHD disorder in our sample is slightly lower than the 34% prevalence of ADHD diagnosis recently reported by Pierpont et al. in subjects with NS.[22] This difference could be partially explained by the more stringent diagnostic criteria for ADHD disorder used in our study, including a direct evaluation of all individuals plus the acquisition of clinical information from both parents and teachers of the involved subjects (CRS-R). Moreover, 3 subjects in our sample (11%) showed only ADHD sub-syndromal traits at the moment of the evaluation, but have been previously diagnosed with ADHD disorder, that was partially compensated at the moment of our assessment.

In order to have a better characterization of the correlation between behavioural phenotype and the genotype (affected gene and type of mutation), we conducted a correlation analysis between the genotype and behavioural test's results. Although the number of the analysed subjects was not sufficient to make a meaningful statistical analysis, ADHD diagnosis looks to be present in individuals carrying any mutation in the three genes.

Possible neurobiological mechanisms underlying the high proportion of ADHD symptoms and syndromes in individuals with NS involve dysfunction of the inhibitory brain circuits on prefrontal cortex and striatum, described in animal models and leading to attention and executive function impairment.[40,41] Also, aberrant signalling through RAS and the MAPK cascade has a relevant role in controlling neuronal cell fate, differentiation and function.[1] In particular, this cascade plays a role in controlling synaptic function (e.g., activity of GABAergic neurons), and changes in hippocampal GABAergic transmission affects learning and memory, while disruption of GABAergic projections from the medium spiny neurons in the striatum alters feedback inhibition of excitatory glutamatergic and the dopaminergic pathways, causing cortical inhibitory-excitatory imbalances.[42]

Symptoms or syndrome of anxiety, including General and Separation Anxiety, and Specific/Social Phobias were present in 37% of the cohort (n = 10; 95% CI = 19–56%), with two individuals (7.4%) showing a DSM-IV anxiety disorder and eight cases (29.7%) exhibiting sub-syndromal anxiety traits. The prevalence of anxiety sub-syndromal traits is 3-times greater than the 10% prevalence reported in community studies of Italian children.[43] This new finding is an important step towards the definition of a psychopathological phenotype of NS and related syndromes, and indicates that emotion regulation might be affected too in this population. This is in line with findings reporting a 50% prevalence of depression in adult samples diagnosed with NS,[44] and with several prospective studies identifying that childhood and adolescent anxiety might precede and predict the development of future adult depressive disorder.[45,46]

Finally, our results confirm the heterogeneity on IQ scores in patients with NS, and are consistent with previous studies finding that the average IQ is generally higher in individuals with NS due to a *SOS1* mutation, compared to mutations in other genes.[10]

4.1. *Limitations*

The main limitation of this study is the small sample size, particularly of individuals carrying *SHOC2* gene mutation. However, all but two subjects have a molecular confirmed diagnosis of NS assuring the precision of the diagnosis. Two subjects show "variants with uncertain significance", however both cases exhibited a NS phenotype and although weak, there is evidence suggesting their possible causative role in pathogenesis.

Also, the short number of subjects with different genetic mutations did not permit to perform a psychopathological genotype/phenotype correlation. Finally, the retrospective and cross-sectional evaluation does not allow the description of a developmental psychopathological profile of this subjects, but should guide future prospective studies involving larger and more homogeneous samples.

5. Conclusions

In 27 individuals with average age 10.4 years (range 6–18 years) with molecular diagnosis of NS or a clinically related disorder we found that 22% of the sample met DSM-IV-TR criteria for ADHD, and 48% showed sub-syndromal ADHD traits, a prevalence that is 7-times greater compared to the 6.9% of reported prevalence of ADHD syndrome and traits in the Italian general population.

Symptoms of anxiety were present in 29.7%, a prevalence that is 3-times greater than the 10% prevalence reported in community studies of Italian children. The present results confirm individuals with NS are at risk to develop a psychopathological disorder or psychiatric disorder, such as ADHD, along their life. It is useful to carry out a screening preschool on attentive functions detecting hyperactivity/impulsivity; it is important to acquire information both from parents and teachers to diagnose and treat a specific disorder as soon as possible.

These data also remark the utility to monitor the anxiety symptoms aiming to perform a precocious diagnosis and plan a specific treatment.

Conflict of interest

None declared.

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