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Parenting Stress Index in Caregivers of Individuals With Noonan Syndrome

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ABSTRACT

Medical professionals frequently underestimate stress level of parents/caregivers of patients with rare disorders as RASopathies, the latter might experience elevated stress levels, with their own health frequently overlooked despite significant responsibilities and hurdles encountered. The aim of this study is to assess the stress experienced by parents of individuals with Noonan syndrome and related conditions. Forty-eight parents (20 fathers; 28 mothers), among the 31 recruited families, completed the Italian version of the Parenting Stress Index–Short Form. Our study shows abnormally elevated scores (≥85° percentile) in 35.4% of parents. Data retrieved from subscales reveal a perception of a difficult child in 25% of cases, a dysfunctional parental-child interaction in 20.8%, a general parental distress in 10.4% of cases, and an elevated overall stress in 18.8% of parents. Questionnaires as the Parenting Stress Index–Short Form are valuable tools to evaluate stress in parents/caregivers of children with RASopathies. Evaluation by professionals is fundamental to support parents and caregivers in managing stressors and to enhance their quality of life and relationships. To prevent stress escalation and parents' burnout, an early assessment to tailor a timely treatment should be introduced as soon as possible as good clinical practice.

1 | Introduction

RASopathies are a group of rare multisystemic neurodevelopmental disorders, caused by a dysregulation in the RAS/MAPK pathway (Karnoub and Weinberg 2008; Mitin, Rossman, and Der 2005), including one of the most extensive group of multiple congenital anomalies syndromes identified (Rauen 2022). Among them, Noonan syndrome (NS, OMIM #PS163950), Noonan syndrome with multiple lentigines (NSML, OMIM #PS151100), Noonan syndrome with Loose Anagen Hair or Mazzanti syndrome (NSLAH #PS607721), Neurofibromatosis type I (NF1, OMIM #162200), Costello syndrome (CS; OMIM #218040), and cardio-facio-cutaneous syndrome (CFCS; OMIM #115150) are rare conditions included in this family. Even though each syndrome presents its own distinctive features, they share several common characteristics (Rauen 2013).

NS ranks among the most prevalent genetic disorders, with an estimated occurrence rate ranging from 1 in 1.000 to 2.500 newborns (Van Der Burgt 2007). Although autosomal recessive inheritance has been demonstrated particularly for *LZTR1* and *SPRED2* gene variants (Johnston et al. 2018; Motta et al. 2021;

Pagnamenta et al. 2019; Tartaglia, Aoki, and Gelb 2022), the condition is mainly inherited in autosomal dominant manner due to germline variants in *PTPN11, SOS1, SOS2, RAF1, BRAF, RIT1, KRAS, NRAS, BRAF, LZTR1, RRAS2*, and *MRAS* genes (Aoki et al. 2016; Motta et al. 2019; Tartaglia, Aoki, and Gelb 2022; Zenker et al. 2022).

Individuals with NS have a distinctive facial gestalt, variable intellectual disability/developmental delay (ID/DD), psychopathological abnormalities (Perrino et al. 2018), ectodermal disorders (Kavamura, Leoni, and Neri 2022), ophthalmologic anomalies (Alfieri et al. 2008), cardiac issues (Leoni et al. 2022), musculoskeletal issues (Stevenson, Viscogliosi, and Leoni 2022), endocrinological anomalies (Siano et al. 2022), and cancer predisposition (Ney et al. 2022).

The psychopathological aspects defining patients with NS has been recently investigated by different researchers (McNeill et al. 2019; Perrino et al. 2018; Roelofs et al. 2020). The most extensive study about the topic reported the presence of a low-to-moderate intelligence and externalizing emotional issues, rather than specific cognitive disorders (McNeill et al. 2019). Indeed, emotion recognition, mentalization and alexithymia emerged as areas of concern in patients with NS (Roelofs et al. 2020). It is known that difficulties in recognizing one's own emotions and those of others may hinder emotion regulation and the building and maintenance of interpersonal relationships, resulting in behavioral problems or psychopathologic conditions (Wingbermühle et al. 2022). Furthermore, decreased social skills, lower levels of attention/ability in executive functions, and high rates of aggression have been described (Naylor et al. 2023).

Since the diagnosis, the required medical assistance and the daily challenges faced by the patients and their support system are a source of distress that might not be recognized by physicians, as their attention is primarily focused toward the child's clinical comorbidities and overall well-being (Scheibner et al. 2024). Consequently, the psychological and socio-economic needs of the family are often underestimated and not adequately explored by care providers (Rietman et al. 2018).

Above-average stress levels have been reported in parents of individuals with special healthcare needs, especially in mothers who are typically being more involved in caregiving and more prone to accept their children's disabilities (De Gaetano et al. 2022; Oelofsen and Richardson 2006; Rietman et al. 2018).

To date, only few studies evaluate the stress/dissatisfaction/discontent/frustration of parents of individuals with NF1, CS, CFCS, NS, and related conditions, and even less explore possible therapeutic opportunities (Esposito et al. 2014; Rietman et al. 2018). In this settings, parent management training (PMT) in families of children with NS has shown some benefit, leading to a decreased stress level and improved previous dysfunctional parent–child interactions (Montanaro et al. 2022).

The aim of the present study is to document the stress experienced by parents of individuals affected by NS and NS-related disorders through the Italian version of the Parent Stress Index-Short Form (PSI-SF) questionnaire, analyzing the total stress levels experienced by parents, their level of distress (regardless from the child), their interaction with their child and perception of them.

Secondarily, we aim to analyze stress levels' differences between mothers and fathers, and the presence of any association with the cognitive level/age of their child.

2 | Methods

2.1 | Patients and Procedure

All participants were recruited at the Centre for Rare Diseases and Birth Defects of Policlinico Universitario Agostino Gemelli, IRCCS in Rome. Parental stress was measured through Parenting Stress Index-Short Form (PSI-SF) (Abidin 1995). During routine follow-up visits at our center, all participants were informed about the aims of this study, the instructions to complete the questionnaires were explained, and privacy was respected.

Inclusion criteria were: (I) having a child with a clinical and molecularly confirmed diagnosis of NS, NS with lose anagen hair (NS-LAH), or NS with multiple lentigines (NSML); (II) having a child with an age comprised between 0 and 25 years old.

Parents of young adults with NS (18–25 years old) were also included in the present study in consideration of the cognitive profile of their children. The latter was assessed through one of three standardized scales used to evaluate IQ (Baron 2005; Roid and Koch 2017; Stroud and Green 2022). The Griffiths III, specific for young children (0–6 years old), analyzes five age-appropriate domains: foundation of learning, language and communication, eye, and hand coordination, personal-social–emotional, and gross-motor skills. The Leiter III is an entirely nonverbal test, which allows the assessment of fluid and nonverbal components of reasoning; it is the preferred evaluation methods for individuals with language disturbances, cerebral damage, or neurodegenerative disorders. The WISC-IV (Wechsler Intelligence Scale for Children—Fourth Edition) is the most specific IQ test for children (> 6 years old to 16 years and 11 months), evaluating fluid intelligence, working memory, and elaboration velocity.

Parents who did not entirely complete the PSI-SF questionnaire were excluded from the analysis.

Data were collected from May 2022 to January 2024. The study was approved by Local EC (ID3717) and written informed consent was signed by all participants.

2.2 | Parenting Stress Index-Short Form

PSI-SF is a questionnaire created for the early identification of the features that may compromise the normal development of the child, as emotional and behavioral disturbances, and parents who have a risk of living their role in a maladaptive manner. The use of this instrument implies that parental stress is due to both intrinsic (subjective characteristics) and extrinsic factors (elements strictly linked to the parental role). The PSI evaluates the

stress that parents experience as the discrepancy between the available resources and the requirements of their role. The common perception of inability and incompetence might be caused by three aspects: the child (difficult temperament, psychopathology etc.), the parents themselves (insecurities, depression, low self-esteem, etc.), and the context (lack or formal/informal support of the social network). In detail, the test analyses the awareness of the parents of their stress/worries, their perception of having a difficult child, and if they have a dysfunctional relationship with the latter.

The PSI-SF comprises 36 items graded on a 5-point Likert scale (strongly agree—strongly disagree). It is based on a theorical model, which analyzes subdimensions of parental stress through the following subscales:

- Parental distress (PD)
- Parent–child dysfunctional interaction (P-CDI)
- Difficult child (DC)

The profile comprises also a defensive response (DIF) subscale, which assesses the level of how the individual responding to the questionnaire gives a more favorable self-image.

Each subscale comprises 12 items with scores ranging from 12 to 60, usually reported as percentiles (Abidin 1995). A total score (ranging from 36 to 180) is obtained by summing up the three subscales. Scores > 80th percentile are considered elevated compared with the normal range in all subscales, whereas scores equal or superior to 90th percentile (85th for the P-CDI subscale) indicate a clinically significant level of stress and should be professionally assessed as soon as possible. Percentile scores between 15th and 80th are considered normal in all subscales.

PD subscale (reported as age-adjusted percentile)—It defines the level of distress that a parent is experiencing in their specific role considering personal issues, independently of the child, the perception of inadequate parental competence, stress associated to the restriction of other vital roles, conflict with the other parent, lack of social support.

P-CDI subscale (reported as age-adjusted percentile)—It analyzes how parents perceive the relationship and the interaction with their child: the perception of the child who does not live up to the expectations, not rewarding interactions, the projections of these feelings on the child, who is considered a negative element in their life, as also the sensation of feeling rejected and exploited by the child, as a stranger. The higher the scores the higher the parents' isolation from their child.

DC subscale (reported as age-adjusted percentile)—It evaluates some aspects of the child behavior and the perception parents have about having a difficult child: child temperament, requiring behaviors, disobedience. High results indicate that the parent is experiencing troubles when facing demanding behaviors of the child.

Total stress (reported as age-adjusted percentile)—It gives an indication of the total level of stress experienced by the individual in their parenting role.

DIF subscale—It assesses the presence of possible bias in the answers (scores ≤ 10). In detail, scores ≤ 10 have different interpretations: the subject is trying to give a more favorable self-image, or the parent is competent in their role and in the management of their responsibility. The psychologist/clinicians will identify the actual situation.

2.3 | Statistical Analysis

Baseline characteristics and outcomes were described using median with interquartile range (IQR) values for numerical variables, while categorical variables were presented using absolute and percentage frequencies. The independent *t*-test or Mann–Whitney *U*-test was used, as appropriate, for comparing differences in continuous variables. The Chi-squared or Fisher's exact test was used, as appropriate, to compare proportions in categorical variables.

Linear regression models investigated the association between type of parent and parental stress outcomes. Multiple linear regression models investigated the association between children's QI and parental stress outcomes, as well as between children's age and parental stress outcomes, adjusted for type of parent. The results of the model analysis were expressed in terms of Beta coefficients, along with their 95% confidence intervals (CIs). A two-sided p-value < 0.05 was considered statistically significant.

All statistical analysis were performed using R version 4.3.2 (31 October 2023) for Windows.

3 | Results

A total of 48 parents/caregivers (28 mothers and 20 fathers) of 31 individuals were enrolled in the present study: 29 with NS and two with NSLAH. Age in NS cohort ranged from 3.7 to 25 years old (median 14.0, IQR 7.0–19.0). Genotypes and cognitive profile of enrolled patients are reported in Tables 1 and 2, respectively. In the entire cohort, three individuals inherited a pathogenic *PTPN11* variant from a parent.

Median and IQR values of percentiles were in the reference range (15th–80th percentiles), except for the third quartile in the DC subscale (> 80th percentile) (Table 3). Despite this, 35.4% (17/48) of interviewed parents reported abnormally elevated scores (≥ 85

TABLE 1 | Genotypes of the study sample.

Affected gene	Number of individuals (%)
PTPN11	20 (64.5%)
KRAS	3 (9.7%)
BRAF	1 (3.2%)
SHOC2	2 (6.5%)
SOS1	4 (12.9%)
LZTR1	1 (3.2%)

percentile) in at least one subscale. In detail, total stress levels >85th percentile was reported in 18.8% (9/48) of parents (four mothers, five fathers). Concerning the other subscales, elevated percentile scores were reported in 10.4% (5/48) of individuals (three mothers, three fathers) in the PD domain, 20.8% (10/48; four mothers, six fathers) in PCDI, and 25% (12/48; four mothers, eight fathers) in the DC area. A defensive response, corresponding to an absolute score in the DIF subscale ≤10, was attributed to 22.9% (11/48) of parents (eight mothers, three fathers).

No significant difference was detected between type of parent and parental stress outcome (Table 3).

No association was detected between the type of parent and total stress, PD, and PCDI subscales (Figure 1a–c), while a significant association was reported in the DC percentile ($p = 0.044$). Fathers were associated with an average increase of 18.6 (95% CI 0.48; 36.73) percentiles compared with mothers (Figure 1d; Table 4).

Given the relatively lower number of patients carrying a pathogenic variant in genes different from *PTPN11*, phenotype–genotype association could not be assessed. However, a description of the genotype of patients in association to the number of parents experiencing high stress levels is shown in Table 5.

No statistically significant associations were identified in the analysis regarding the relationship between children's IQ and percentile values for each domain of the PSI-SF. However, it was observed that parents of children's IQ scores at the lower limits of normal (LLN) showed significantly lower scores in the DC domain ($p = 0.015$) compared to peers of children in normal range (Table S1).

No significant association was detected between the child's age and parental stress outcome in the adjusted linear regression analysis ($p > 0.05$) (Table S2).

TABLE 2 | Cognitive profile in the study sample.

IQ range[a]	Level of intellectual disability	Number of patients (%)
<40	Severe	0 (0%)
40–54	Moderate	1 (3.2%)
55–69	Mild	6 (19.4%)
70–84	Lower limits of normal	11 (35.5%)
>84	Normal range	12 (38.7%)
—	Missing	1 (3.2%)

[a]IQ: intelligence quotient was measured through either Griffith, Leiter, or WISC scale.

4 | Discussion

Since the diagnosis communication, the management of a child affected by rare disorders or chronic illness has significant consequences on the psychological well-being of the other family members, in particular on the parents/caregivers (Naylor et al. 2023). Collaboration and active engaging of the family is fundamental to ensure effective habilitative programs and the consequent well-being of the individuals (De Gaetano et al. 2022). Moreover, adjusting and adapting skills are required throughout child's life.

Previous studies assessing parental stress level through the PSI-SF, described higher stress levels in parents of children with developmental disabilities compared to parents of physiologically developing children (Oelofsen and Richardson 2006; Herring et al. 2006; McStay et al. 2014; Woolfson and Grant 2006). Several factors may also contribute to worsen parental stress, such as socio-economic status, behavioral issues, the age of the caregiver, and the intensity of medical care needs (Herring et al. 2006; McStay et al. 2014).

In detail, concerning RASopathies, very few studies closely investigated parenting stress (Draucker et al. 2017; Esposito et al. 2014; Ganetsos et al. 2020; Montanaro et al. 2022; Pierpont and Wolford 2016; Rietman et al. 2018) (see Table S4).

In one study, mothers of children with NF1, assessed through the PSI-SF, experienced higher stress than mothers of healthy/nonsyndromic children, with significantly higher scores in the difficult child subscale (Esposito et al. 2014). Another report described high levels of maternal stress, highlighting the importance of the environment in the management of NF1 during developmental age. (Esposito et al. 2014). Interestingly, NF1 parent and family functioning was described as comparable with control groups by other authors (Reiter-Purtill et al. 2007).

TABLE 3 | Median (IQR) values for each domain of the PSI-SF.

	All ($n = 48$)	Fathers ($n = 20$)	Mothers ($n = 28$)	p
Total stress[a]	42.5 (25.0; 60.0)	55.0 (43.0; 81.3)	35.0 (23.8; 56.3)	0.084
PD[a]	30.0 (15.0; 55.0)	45.0 (20.0; 70.3)	25.0 (10.0; 51.3)	0.121
PCDI[a]	52.0 (35.0; 75.0)	55.0 (35.0; 95.0)	42.5 (28.8; 70.0)	0.179
DC[a]	52.5 (25.0; 85.0)	72.5 (43.8; 86.3)	40.0 (20.0; 71.3)	0.054
DIF[b]	14.0 (11.0; 17.0)	13.5 (12.0; 18.5)	14.0 (9.8; 16.3)	0.482

Note: p-value <0.05 was considered statistically significant.
Abbreviations: DC: difficult child; DIF: defensive response; PCDI: parent–child dysfunctional interaction; PD: parent distress.
[a]Percentile.
[b]Score as absolute value.

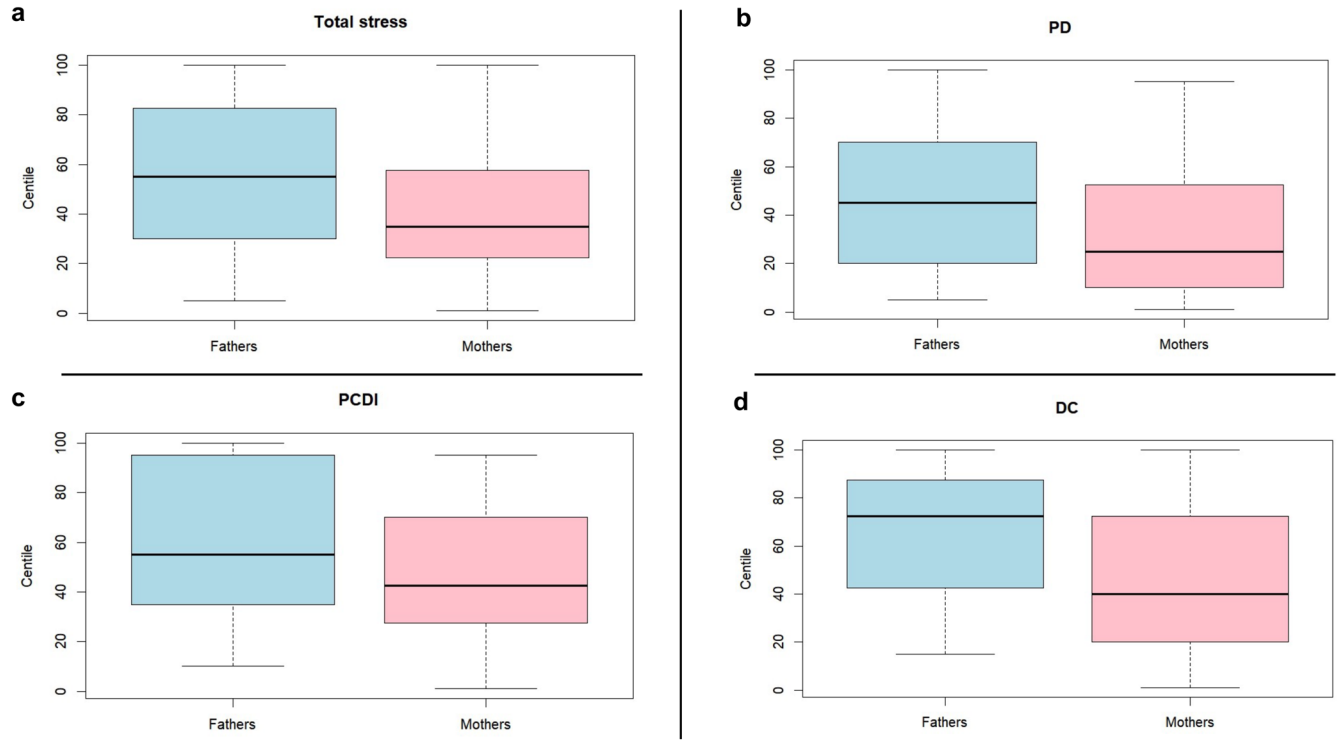

FIGURE 1 | Boxplots representing percentile scores of fathers and mothers in the total stress, PD, PCDI, and DC domains.

TABLE 4 | Linear models for exploring the association between type of parent and percentile values for each domain of the PSI-SF.

n = 48	Beta (95% CI) fathers vs. mothers	*p*
Total stress	14.93 (−1.75; 31.60)	0.078
PD	12.29 (−3.94; 28.51)	0.134
PCDI	11.81 (−5.51; 29.12)	0.177
DC	18.61 (0.48; 36.73)	0.044[a]

Abbreviations: DC: difficult child; PCDI: parent–child dysfunctional interaction; PD: parent distress.
[a]*p*-value < 0.05 was considered statistically significant.

TABLE 5 | Total number of parents (mothers–fathers) with scores ≥85th percentile in total stress, PD, PCDI, and DC, associated to the genotype of their children.

Genotype	Total stress	PD	PCDI	DC
PTPN11	4 (2–2)	3 (1–2)	4 (2–2)	7 (3–4)
KRAS	2 (1–1)	1 (1–0)	3 (1–2)	2 (1–1)
BRAF	2 (1–1)	1 (1–0)	2 (1–1)	2 (1–1)
SHOC2	1 (0–1)	0	1 (0–1)	0
SOS1	0	0	0	1 (0–1)

Abbreviations: DC: difficult child; PCDI: parent–child dysfunctional interaction; PD: parent distress.

Ganetsos et al. (2020) observed in a cohort of individuals with Costello and cardio-facio-cutaneous syndrome that stress level was negatively influenced by the young age of the child, the young age of caregivers, and the greater numbers of children to take care of in the family setting. Moreover, the expansion and the strengthening of a social support system could decrease stress levels, fostering more positive parenting behaviors.

Coherently, in a recent survey involving family members of individuals with NS, it was observed that parents' concerns diminished over time, consistently with the reduction of intensity of medical issues (Coveney and Lambert 2023).

Other studies have assessed how young people with NF1 and their families experience a wide range of concerns and stress related to health, quality of life, different expression of symptoms, and uncertainty linked to the disease course (Draucker et al. 2017; Pierre-Louis et al. 2018).

In the present study, we detected an elevated stress levels in at least one domain of the PSI-SF in more than one third of interviewed parents (35.4%). In detail, high total stress level was reported in 18.8% of parents, an elevated parental distress in 10.4% (PD domain), a dysfunctional parent–child interaction in 20.8% (PCDI domain), and a perception of having a difficult child in 25% (DC domain). Such high scores highlight the importance of routine assessment and monitoring of psychological health and stress levels in families of individuals affected by NS.

Furthermore, differently from what has been previously reported concerning RASopathies (Ganetsos et al. 2020), in our cohort no significant association was detected between higher stress levels and patients' age. This finding may be due to the milder clinical and psychopathological issues characterizing NS

compared to other disorders of the Ras/MAPK pathway such as Costello and cardio-facio-cutaneous syndrome.

We have found a significant association between cognitive profile and DC domain's scores. High scores in such subscale suggest the need of a psychological evaluation in order to provide a personalized educational plan and to improve outcomes of parents and children.

A comparison between the stress levels in interviewed caregivers has been also performed in our study, detecting a significant higher stress level in the DC domain in mothers compared with fathers. We speculate this may be due to several factors, such as the lower number of fathers investigated compared with mothers as well as the stronger impact of children care-management on mothers' life compared with fathers.

As stated by Hassall, Rose, and McDonald (2005) about children with intellectual impairment, we speculate that another factor influencing parental stress in RASopathies might be the severity of behavioral disorders. Anyway, given the relatively mild nature of behavioral disturbances in individuals with NS compared with other RASopathies (e.g., CS, CFCS), future studies comparing PSI-SF scores among parents of individuals with different RASopathies will be necessary.

Recently, the positive effects of PMT have been evaluated in a small cohort of parents of young children with NS through questionnaires as the PSI-SF. Improvements in the PSI-SF PCDI, DC, and total stress subscales were observed after PMT, especially in mothers, who were referred as feeling more discouraged before the intervention (Montanaro et al. 2022).

Preventing or addressing parental distress is of paramount importance as it affects not only parents' health but also that of their children. This is true for NS and related conditions, as also for RASopathies and in general for other rare disorders.

Given the availability of numerous nonpharmacological treatment strategies (e.g., cognitive behavioral therapy, PMT, support groups, and family support services) to support caregivers of children with RASopathies and other rare conditions dealing with stress, it is of utmost importance to introduce psychological screening programs aiming at an early detection and management of stress level in these vulnerable families (Lancaster et al. 2023).

Our preliminary data suggest that further studies evaluating parental stress and mental health concerns will be essential to understand which specific treatment strategy might offer greater impact for each RASopathy condition.

4.1 | Study Limitations

This study has potential limitations. Currently, there is a paucity of data validating the use of the PSI-SF in rare disorders. Furthermore, as most NS patients in the examined cohort carry a *PTPN11* mutation, no genotype–phenotype correlation could be assessed. Moreover, the sample size is limited due to the rarity of the syndrome. Finally, it was not possible to collect questionnaires from both parents in the whole cohort.

5 | Conclusion

Results from PSI-SF in our cohort of parents/caregiver of NS patient showed elevated scores in at least one of the PSI-SF areas in 35.4% of recruited individuals, with high total stress levels observed in 18.8%. Such findings support the importance of early evaluation to promptly implement treatment strategies to prevent caregiver burnout and related health issues.

Questionnaires, like the PSI-SF in our case, are valuable screening instruments to assess stress in parents of children with RASopathies and rare disorder. Our data will need further validation with future studies investigating both cognitive, psychopathological and adaptive profile in patients with NS.

Longitudinal evaluation by professionals remains crucial for accurately characterizing the condition and intervening in the earliest occasion.

Author Contributions

L.P.: conceptualization (lead), data curation (lead), project administration (lead); writing — original draft (equal); methodology (lead). **G.V.:** data curation (lead); writing — original draft (equal); writing — review and editing (equal); methodology (supporting). **V.T.:** data curation (supporting); writing — review and editing (equal);visualization (supporting). **C.B.:** methodology (supporting); writing — review and editing (equal). **D.P.R.C.:** methodology (supporting); writing — review and editing (equal). **I.C.:** methodology (supporting); writing — review and editing (equal). **P.A.:** methodology (supporting); writing — review and editing (equal). **N.L.:** formal analysis (lead); validation (lead), visualization (supporting); writing — original draft (supporting); writing — review and editing (equal). **R.P.:** formal analysis (supporting); validation (lead), visualization (supporting); writing — review and editing (equal). **G.Z.:** writing — review and editing (equal), supervision (equal). **C.L.:** funding acquisition (lead); conceptualization (supporting); writing — original draft (supporting); writing — review and editing (equal). All authors reviewed and accepted the final version of the manuscript.

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Consent

Written informed consent was obtained from the patients to publish this paper.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Abidin, R. R. 1995. *Parenting Stress Index: Professional Manual*. 3rd ed. Odessa, FL: Psychological Assessment Resources.

Alfieri, P., L. Cesarini, G. Zampino, et al. 2008. "Visual Function in Noonan and LEOPARD Syndrome." *Neuropediatrics* 39, no. 6: 335–340. https://doi.org/10.1055/s-0029-1216354.

Aoki, Y., T. Niihori, S. Inoue, and Y. Matsubara. 2016. "Recent Advances in RASopathies." *Journal of Human Genetics* 61, no. 1: 33–39. https://doi.org/10.1038/jhg.2015.114.

Baron, I. S. 2005. "Test Review: Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)." *Child Neuropsychology* 11, no. 5: 471–475. https://doi.org/10.1080/09297040590951587.

Coveney, K., and I. Lambert. 2023. "Living With Noonan Syndrome: Report of an Online Survey." https://hdl.handle.net/2134/22361122.v1.

De Gaetano, K., D. Saviola, D. Brunetti, and A. De Tanti. 2022. "The Importance of Assessing Parent Stress in Families With Children With Severe Neuromotor and Intellectual Disability – A Pilot Study." *Applied Neuropsychology: Child* 11, no. 4: 804–810. https://doi.org/10.1080/21622965.2021.1971525.

Draucker, C. B., K. Nutakki, J. W. Varni, and N. L. Swigonski. 2017. "The Health-Related Quality of Life of Children, Adolescents, and Young Adults With Neurofibromatosis Type 1 and Their Families: Analysis of Narratives." *Journal for Specialists in Pediatric Nursing* 22, no. 2: e12174. https://doi.org/10.1111/jspn.12174.

Esposito, M., R. Marotta, M. Roccella, et al. 2014. "Pediatric Neurofibromatosis 1 and Parental Stress: A Multicenter Study." *Neuropsychiatric Disease and Treatment* 141: 141–146. https://doi.org/10.2147/NDT.S55518.

Ganetsos, A., E. Farrelly, P. Magoulas, and D. A. Stevenson. 2020. "Stress and Coping in Caregivers of Children With RASopathies: Assessment of the Impact of Caregiver Conferences." *Journal of Pediatric Genetics* 9, no. 4: 235–242. https://doi.org/10.1055/s-0040-1712178.

Hassall, R., J. Rose, and J. McDonald. 2005. "Parenting Stress in Mothers of Children With an Intellectual Disability: The Effects of Parental Cognitions in Relation to Child Characteristics and Family Support." *Journal of Intellectual Disability Research* 49, no. 6: 405–418. https://doi.org/10.1111/j.1365-2788.2005.00673.x.

Herring, S., K. Gray, J. Taffe, B. Tonge, D. Sweeney, and S. Einfeld. 2006. "Behaviour and Emotional Problems in Toddlers With Pervasive Developmental Disorders and Developmental Delay: Associations With Parental Mental Health and Family Functioning." *Journal of Intellectual Disability Research* 50, no. 12: 874–882. https://doi.org/10.1111/j.1365-2788.2006.00904.x.

Johnston, J. J., J. J. Van Der Smagt, J. A. Rosenfeld, et al. 2018. "Autosomal Recessive Noonan Syndrome Associated With Biallelic LZTR1 Variants." *Genetics in Medicine* 20, no. 10: 1175–1185. https://doi.org/10.1038/gim.2017.249.

Karnoub, A. E., and R. A. Weinberg. 2008. "Ras Oncogenes: Split Personalities." *Nature Reviews Molecular Cell Biology* 9, no. 7: 517–531. https://doi.org/10.1038/nrm2438.

Kavamura, M. I., C. Leoni, and G. Neri. 2022. "Dermatological Manifestations, Management, and Care in RASopathies." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 190, no. 4: 452–458. https://doi.org/10.1002/ajmg.c.32027.

Lancaster, K., A. Bhopti, M. L. Kern, R. Taylor, A. Janson, and K. Harding. 2023. "Effectiveness of Peer Support Programmes for Improving Well-Being and Quality of Life in Parents/Carers of Children With Disability or Chronic Illness: A Systematic Review." *Child: Care, Health and Development* 49, no. 3: 485–496. https://doi.org/10.1111/cch.13063.

Leoni, C., R. Blandino, A. B. Delogu, et al. 2022. "Genotype-Cardiac Phenotype Correlations in a Large Single-Center Cohort of Patients Affected by RASopathies: Clinical Implications and Literature Review." *American Journal of Medical Genetics Part A* 188, no. 2: 431–445. https://doi.org/10.1002/ajmg.a.62529.

McNeill, A. M., R. L. Hudock, A. M. H. Foy, et al. 2019. "Emotional Functioning Among Children With Neurofibromatosis Type 1 or Noonan Syndrome." *American Journal of Medical Genetics Part A* 179, no. 12: 2433–2446. https://doi.org/10.1002/ajmg.a.61361.

McStay, R. L., C. Dissanayake, A. Scheeren, H. M. Koot, and S. Begeer. 2014. "Parenting Stress and Autism: The Role of Age, Autism Severity, Quality of Life and Problem Behaviour of Children and Adolescents With Autism." *Autism* 18, no. 5: 502–510. https://doi.org/10.1177/1362361313485163.

Mitin, N., K. L. Rossman, and C. J. Der. 2005. "Signaling Interplay in Ras Superfamily Function." *Current Biology* 15, no. 14: R563–R574. https://doi.org/10.1016/j.cub.2005.07.010.

Montanaro, F. A. M., P. Alfieri, C. Caciolo, et al. 2022. "Neuropsychological Features in RASopathies: A Pilot Study on Parent Training Program Involving Families of Children With Noonan Syndrome." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 190, no. 4: 510–519. https://doi.org/10.1002/ajmg.c.32025.

Motta, M., G. Fasano, S. Gredy, et al. 2021. "SPRED2 Loss-Of-Function Causes a Recessive Noonan Syndrome-Like Phenotype." *American Journal of Human Genetics* 108, no. 11: 2112–2129. https://doi.org/10.1016/j.ajhg.2021.09.007.

Motta, M., M. Fidan, E. Bellacchio, et al. 2019. "Dominant Noonan Syndrome-Causing *LZTR1* Mutations Specifically Affect the Kelch Domain Substrate-Recognition Surface and Enhance RAS-MAPK Signaling." *Human Molecular Genetics* 28, no. 6: 1007–1022. https://doi.org/10.1093/hmg/ddy412.

Naylor, P. E., J. L. Bruno, S. B. Shrestha, et al. 2023. "Neuropsychiatric Phenotypes in Children With Noonan Syndrome." *Developmental Medicine and Child Neurology* 65, no. 11: 1520–1529. https://doi.org/10.1111/dmcn.15627.

Ney, G., A. Gross, A. Livinski, C. P. Kratz, and D. R. Stewart. 2022. "Cancer Incidence and Surveillance Strategies in Individuals With RASopathies." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 190, no. 4: 530–540. https://doi.org/10.1002/ajmg.c.32018.

Oelofsen, N., and P. Richardson. 2006. "Sense of Coherence and Parenting Stress in Mothers and Fathers of Preschool Children With Developmental Disability." *Journal of Intellectual & Developmental Disability* 31, no. 1: 1–12. https://doi.org/10.1080/13668250500349367.

Pagnamenta, A. T., P. J. Kaisaki, F. Bennett, et al. 2019. "Delineation of Dominant and Recessive Forms of *LZTR1*-Associated Noonan Syndrome." *Clinical Genetics* 95, no. 6: 693–703. https://doi.org/10.1111/cge.13533.

Perrino, F., S. Licchelli, G. Serra, et al. 2018. "Psychopathological Features in Noonan Syndrome." *European Journal of Paediatric Neurology* 22, no. 1: 170–177. https://doi.org/10.1016/j.ejpn.2017.09.009.

Pierpont, E. I., and M. Wolford. 2016. "Behavioral Functioning in Cardiofaciocutaneous Syndrome: Risk Factors and Impact on Parenting Experience." *American Journal of Medical Genetics Part A* 170, no. 8: 1974–1988. https://doi.org/10.1002/ajmg.a.37725.

Pierre-Louis, C., T. Heinhuis, E. Riklin, and A. Vranceanu. 2018. "Challenges Associated With Parenting Youth With Neurofibromatosis: A Qualitative Investigation." *American Journal of Medical Genetics Part A* 176, no. 4: 959–968. https://doi.org/10.1002/ajmg.a.38640.

Rauen, K. A. 2013. "The RASopathies." *Annual Review of Genomics and Human Genetics* 14, no. 1: 355–369. https://doi.org/10.1146/annurev-genom-091212-153523.

Rauen, K. A. 2022. "Defining RASopathy." *Disease Models & Mechanisms* 15, no. 2: dmm049344. https://doi.org/10.1242/dmm.049344.

Reiter-Purtill, J., E. K. Schorry, A. M. Lovell, K. Vannatta, C. A. Gerhardt, and R. B. Noll. 2007. "Parental Distress, Family Functioning, and Social

Support in Families With and Without a Child With Neurofibromatosis 1." *Journal of Pediatric Psychology* 33, no. 4: 422–434. https://doi.org/10.1093/jpepsy/jsm077.

Rietman, A. B., H. Van Helden, P. H. Both, et al. 2018. "Worries and Needs of Adults and Parents of Adults With Neurofibromatosis Type 1." *American Journal of Medical Genetics Part A* 176, no. 5: 1150–1160. https://doi.org/10.1002/ajmg.a.38680.

Roelofs, R. L., E. Wingbermühle, P. T. Van Der Heijden, et al. 2020. "Personality and Psychopathology in Adults With Noonan Syndrome." *Journal of Clinical Psychology in Medical Settings* 27, no. 2: 256–267. https://doi.org/10.1007/s10880-019-09659-7.

Roid, G. H., and C. Koch. 2017. "Leiter-3: Nonverbal Cognitive and Neuropsychological Assessment." In *Handbook of Nonverbal Assessment*, edited by R. S. McCallum, 127–150. New York, NY: Springer International Publishing. https://doi.org/10.1007/978-3-319-50604-3_8.

Scheibner, C., M. Scheibner, F. Hornemann, et al. 2024. "Parenting Stress in Families of Children With Disabilities: Impact of Type of Disability and Assessment of Attending Paediatricians." *Child: Care, Health and Development* 50, no. 1: e13193. https://doi.org/10.1111/cch.13193.

Siano, M. A., R. Pivonello, M. Salerno, et al. 2022. "Endocrine System Involvement in Patients With RASopathies: A Case Series." *Frontiers in Endocrinology* 13: 1030398. https://doi.org/10.3389/fendo.2022.1030398.

Stevenson, D. A., G. Viscogliosi, and C. Leoni. 2022. "Bone Health in RASopathies." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 190, no. 4: 459–470. https://doi.org/10.1002/ajmg.c.32020.

Stroud, L., and E. Green. 2022. *Griffiths III – A Case Study Book for Practitioners*. Göttingen, Germany: Hogrefe Publishing GmbH. https://books.google.it/books?id=lqWbEAAAQBAJ.

Tartaglia, M., Y. Aoki, and B. D. Gelb. 2022. "The Molecular Genetics of RASopathies: An Update on Novel Disease Genes and New Disorders." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 190, no. 4: 425–439. https://doi.org/10.1002/ajmg.c.32012.

Van Der Burgt, I. 2007. "Noonan Syndrome." *Orphanet Journal of Rare Diseases* 2, no. 1: 4. https://doi.org/10.1186/1750-1172-2-4.

Wingbermühle, E., R. L. Roelofs, W. Oomens, et al. 2022. "Cognitive Phenotype and Psychopathology in Noonan Syndrome Spectrum Disorders Through Various Ras/MAPK Pathway Associated Gene Variants." *Journal of Clinical Medicine* 11, no. 16: 4735. https://doi.org/10.3390/jcm11164735.

Woolfson, L., and E. Grant. 2006. "Authoritative Parenting and Parental Stress in Parents of Pre-School and Older Children With Developmental Disabilities." *Child: Care, Health and Development* 32, no. 2: 177–184. https://doi.org/10.1111/j.1365-2214.2006.00603.x.

Zenker, M., T. Edouard, J. C. Blair, and M. Cappa. 2022. "Noonan Syndrome: Improving Recognition and Diagnosis." *Archives of Disease in Childhood* 107, no. 12: 1073–1078. https://doi.org/10.1136/archdischild-2021-322858.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.