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Neurodevelopmental profile in children born to mothers affected by systemic sclerosis

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ABSTRACT

Background: Systemic sclerosis (SSc) is a chronic immune-mediated connective tissue disease that can affect women of childbearing age. The long-term outcomes of their offspring remain poorly explored. Aim of this study was to detail the neurodevelopmental profile of children born to SSc mothers.

Methods: Twenty children (mean age: 96 ± 4.32 months; 10 males) born to SSc mothers were enrolled. We collected data on clinical history, neurological examination, cognitive profile and adaptive behavior in all subjects. According to the chronological age, we also investigated quality of life, behavioral characteristics, psychological functioning and self-image.

Results: All the children had normal neurological examination, cognitive profile and adaptive functioning, except for one (5 %) who suffered from Autism Spectrum Disorder. An important discrepancy was observed between parental and child opinion regarding the perception of quality of life, more compromised in the latter. We documented a risk for internalizing behavioral problems in 2 cases (10 %), for externalizing problems in 3 (15 %), for both in 1 (5 %) and for social and out-of-school activities in 5 (25 %). As regards psychological functioning, evaluated in 11 children, three (28 %) were at risk for anxiety, 1 (9 %) for depressive disorders and other 4 (36 %) for somatic disturbances. Emotional fragility and poor competence in metabolizing one's emotional experiences were observed in 9 out of the 13 subjects assessed (70 %).

Conclusions: Children born to SSc women exhibit normal cognitive and adaptive abilities but an increased vulnerability to psychopathological problems and fragility in social functioning. These observations might reflect that children need to feel mature to accept maternal chronic disease that, in turn, may hinder support for offspring's social and emotional development.

1. Introduction

Systemic sclerosis (SSc) is a rare autoimmune systemic condition, classified among connective tissue diseases affecting women during perimenopausal age [1,2].

The earlier phase of the pathogenetic pathway is vasculopathy, which is mirrored by the appearance of Raynaud's phenomena, and is currently recognized as a key-process further activating the following steps, represented by immune activation and fibrosis [1]. The disease has a chronic and often progressive course characterized by increased skin thickness, important functional limitations, mainly affecting the hands and aesthetical changes, especially involving the face. Gastrointestinal, musculoskeletal, cardiac and pulmonary involvement characterize the clinical picture, even if in different combinations and with variable severity.

Regarding reproductive implications of SSc, the first issue is represented by the rarity of the disease itself and the rarity of its onset during reproductive age, thus resulting in a limited number of pregnancies reported in existing literature. Moreover, for a long-time young women with SSc have been discouraged from becoming pregnant, because of the

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increased risk of maternal and fetal adverse outcomes, such as risk for disease progression or symptom exacerbation, miscarriage, intrauterine growth retardation, preterm delivery, and low birth weight [1,3]. Only in the last decades, the improvement in SSc knowledge, encompassing pregnancy implications and reproductive issues, has allowed an increasing number of patients to carry out successful pregnancies [4]. Information on the long-term outcome of the children is currently lacking but is crucial for providing a comprehensive counseling for these patients.

The aim of the study was to detail the neurodevelopmental profile, the cognitive level, the adaptive functioning, the quality of life, the behavioral characteristics and the self-image in a cohort of children born to mothers affected by SSc. An early identification of any possible vulnerabilities in the neurodevelopmental and psychic profiles may help clinicians ensure adequate preventive and supportive measures to women with SSc and their children.

2. Materials and methods

Twenty children (mean age: 96 ± 4.32 months, range 13–204; 10 males) born to mothers affected by SSc, followed-up at Rheumatology and Clinical Immunology Unit, ERN ReCONNET, ASST Spedali Civili of Brescia, Italy, were enrolled for the present study. Inclusion criteria were: maternal diagnosis of SSc according to 2013 EULAR/ACR criteria [5]; age from birth to 18 years; ability to read, speak and understand Italian. Clinical evaluations were carried out by a Child Neuropsychiatrist at Child Neurology and Psychiatry Unit, ASST Spedali Civili of Brescia, Italy, between April 2022 and March 2023.

We collected demographic (age, sex) and clinical data (pregnancy, drugs administered to mothers during pregnancy, gestational age, delivery, birth weight and length, head circumference, perinatal period, and neurodevelopment milestones) from parental interviews. Along with neurological examination, subjects underwent a detailed assessment of the neurodevelopmental/cognitive level, the adaptive functioning, the emotional and behavioral characteristics, the quality of life and the mental health, according to chronological age.

The neurodevelopmental profile was assessed using the Griffiths-III [6] and the cognitive quotient with the Wechsler Scales according to subject's age [7–9]. Full-scale intelligence quotient (FSIQ), verbal comprehension/verbal intelligence quotient (VCI/VIQ), perceptual reasoning/performance intelligence quotient (PRI/PIQ), working memory (WMI), and processing speed index (PSI) scores were collected. All the quotients are reported in standard scores (mean 100, SD 15) and defined as follows: more than −1 DS, normal; between −1 and −2 DS, borderline; and <−2 DS, delay.

Adaptive functioning was evaluated using the Vineland Adaptive Behavior Scales-II (VABS-II) [10], a questionnaire completed by parents that covers four domains: communication, socialization, daily living skills, and motor skills. Centile score < 5 was considered as a cut-off for adaptive disorders.

As regards emotional-behavioral characteristics, we used age-appropriate versions of the Child Behavior Checklist (CBCL), 1½-5 [11,12] or 6–18 years [13], and the Youth Self Report (YSR), 11–18 years [14] to assess children's emotional, behavioral, and social problems as observed by the parents (CBCL) and self-evaluated (YSR). Composite scales (internalizing, externalizing, and total problems) and syndrome scales (CBCL 1½-5: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior; CBCL 6–18 and YSR: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior) are obtained from the item scores, categorized as "normal," "borderline," or "clinically significant" according to the tool kit software standards.

The Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0) [15] was used to evaluate the health-related quality of life (HRQOL) and comprises parallel child self-report and parent-report formats. The scale consists of 23 items, each with 5 multiple choices, to investigate physical, emotional, social, and school functioning areas. The subscales lead to a total score, a Physical Health Summary Score (obtained from the physical functioning subscale) and a Psychological Health Summary Score (from the emotional, social, and school functioning subscales). The scores are converted on a scale from 0 to 100 with higher scores indicating better HRQOL.

As regards mental health, we chose the Self-administered psychiatric scales for children and adolescents (Scale Psichiatriche di Autosomministrazione per Fanciulli e Adolescenti, SAFA) [16] for detecting symptoms included in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [17]. For the purpose of this study, we used the following scales: SAFA-A for Anxiety symptoms (4 subscales: generalized anxiety, social anxiety, separation anxiety, school anxiety), SAFA-D for Depressive symptoms (7 subscales: depression, anhedonia, irritability, sense of inadequacy, insecurity, sense of guilty, hopelessness), and SAFA-S for Somatic complaints (2 subscales: somatic symptoms, hypochondria). For each subscale, T score is obtained by raw score and defined as pathological when >69 and borderline when $60 < T < 69$.

Finally, the Human Figure Drawing test (HFDT) [18,19] is a projective test used to assess the child's psychological maturity and the variables of his/her personality. Drawings were evaluated according to three main levels of interpretation (graphic, formal structures, and content one). For affectivity, we considered the following characteristics among those suggested by Machover [20]: centeredness on paper, figure size, line characteristics, arm and leg positioning, age, and gender assigned to figure. Summary of the evaluations is reported in Table 1.

The study was conducted in accordance with the ethical guidelines set forth by the Declaration of Helsinki and was approved by the Ethical Committee of ASST Spedali Civili in Brescia (NP 5843), Italy. Written informed consent was obtained from parents of the children.

2.1. Statistical analysis

A descriptive analysis of the findings was performed. Qualitative variables were analyzed in terms of number and percentage, while quantitative data were reported as mean, standard deviation, and range.

3. Results

3.1. Anamnestic data

Seventeen children (85 %) were born after SSc diagnosis and the remaining 3 (15 %) before.

According to mother interviews, pregnancy was uneventful in 13 (65 %) cases; in the remaining subjects, group B *Streptococcus* infection occurred in 4 cases (20 %), preeclampsia in 1 (5 %, occurred at 32 weeks and leading to preterm birth), urosepsis in 1 (5 %) and oligohydramnios in 1 (5 %). Sixteen (80 %) children were born at term, 1 (5 %) at *late preterm* (35 weeks of gestation), and 3 (15 %) at *very preterm* (31–32 weeks of gestation; 2 were twins). Perinatal complications were present in all preterm newborns and in other 8 subjects (60 %) and characterized by

Table 1
Summary of neuropsychiatric evaluations.

Evaluation	Material	Number of children
Neurodevelopmental/cognitive level	Griffiths-III	3
	Wechsler Scales	17
Adaptive functioning	VABS-II	20
Emotional-behavioral characteristics	CBCL	20
	YSR	6
Quality of life	PedsQL	14
Mental health	SAFA	11
Emotional fragility	HFDT	13

perinatal infection (5 neonates, 42 %), respiratory distress (4, 33 %), sinus arrhythmia (2, 17 %), and excessive weight loss at birth (1, 8 %). Details are reported in Table 2.

All the children appropriately acquired the gross-motor milestones. Eighteen children (90 %) normally developed communication and language skills. One subject (5 %) produced the first words at 17 months (no information on subsequent language evolution is available, since the infant was 18 months at the time of the evaluation). The remaining one child, called "patient number 3" (P3) (5 %), produced the first word at 20 months with subsequent failure to develop communication and language skills due to the Autism Spectrum Disorder (ASD) diagnosed at 3 years of age according to DSM-V criteria. Four children (20 %) presented with feeding disorders (weaning difficulties: 3 cases; avoidant/restrictive food intake disorder: 1, P3) and 9 (45 %) one or more sleep disorders (nocturnal awakenings: 5 cases; insomnia or difficulty initiating sleep: 2; parasomnia and pavor nocturnus: 2; snoring: 1).

3.2. Direct assessment

No abnormalities concerning cranial nerve, head circumference, muscle strength, tone and bulk, reflexes, and gait were detected at neurological examination.

All the sample had normal neurodevelopmental/cognitive profile, except for P3. In particular, all the 3 cases evaluated with Griffiths-III obtained normal score on developmental quotient (DQ) and on the following subscales: foundation of learning, hand-eye coordination, personal-social-emotional, and gross-motor; one had a delay in language and communication subscale. As regard cognitive evaluation, performed in the other 17 children, FSIQ, VIQ/VCI and PIQ/PRI were normal in 16 cases (94 %). P3 showed deficient scores at FSIQ, VIQ, PIQ. PSI, evaluated in 14 children, was normal in 12 (86 %), borderline in one and delayed in P3. WMI, assessed in 11 cases, was normal in all the children.

Adaptive functioning was impaired only in P3 (5%), who had difficulties in all the VABS-II domains: total (4° percentile), communication (6°), socialization (6°), daily living skills (4°). Considering the remaining subjects, mean total score was 68.4 ± 21 (range 19–96), communication 56.6 ± 23.6 (range 9–92), socialization 65.5 ± 23.6 (range 21–92), daily living skills 63.3 ± 29.4 (range 12–96).

At CBCL composite scales, 1 child (5 %) had risk score in total problems, 2 (10 %) in internalizing problems, and 3 (15 %) in externalizing problems. See Figs. 1 and 2 for details on syndrome scales. It is worth noting that, at CBCL 6–18, 4 subjects out of 12 (33 %) also presented with risk score for social and out-of-school activities. This finding was partially confirmed at YSR, completed by 6 adolescents: four (67 %) scored at risk for social and out-of-school activities (three were those at risk at CBCL 6–18).

As regards HRQOL, PEDSQL questionnaire was administered to 18 parents (90 %) and 14 children (70 %). An important discrepancy was observed between parental opinion and what children reported about their perception of a compromised quality of life: specifically, the former reported higher mean scores (indicating a better HRQOL) compared to the latter, among all in physical and emotional functioning. Mean scores of each subscale are reported in Fig. 3.

SAFA questionnaires were administered to 11 (55 %) children in relation to age. At SAFA-A general scale, the mean total score was 45.3 ± 7.2 (range: 38–60), at SAFA-D general scale 48.4 ± 6.2 (range: 37–58), and at SAFA-S general scale 44.2 ± 10.4 (range: 34–71). T scores are reported in Table 3.

Finally, as regards HFDT (administered to 13 children), the graphic level of the drawings was globally characterized by an immature graphic trait: in 10 (77 %) cases, lines were discontinuous and full of erasures, shading and blackening that can be interpreted as the expression of

Table 2
Anamnestic data.

	Number of children (%)
Pregnancy complications	7 (35)
Preterm birth	4 (20)
Caesarean section	11 (55)
Birth weight, g	
Mean ± SD	3013 ± 824.3
Range	1390–4330
Birth length, cm	
Mean ± SD	48.7 ± 3.6
Range	41–54
Head circumference, cm	
Mean ± SD	33.3 ± 2.2
Range	29–37
Perinatal complications	12 (60 %)

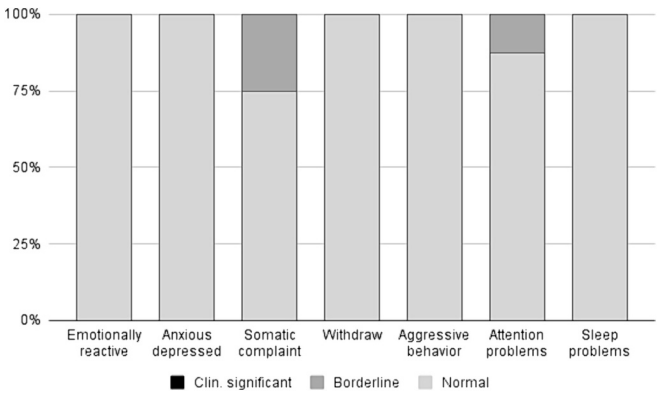

Fig. 1. CBCL ½–5 syndrome scale (administered in 8 cases).
Abbreviation: Clin., clinically.

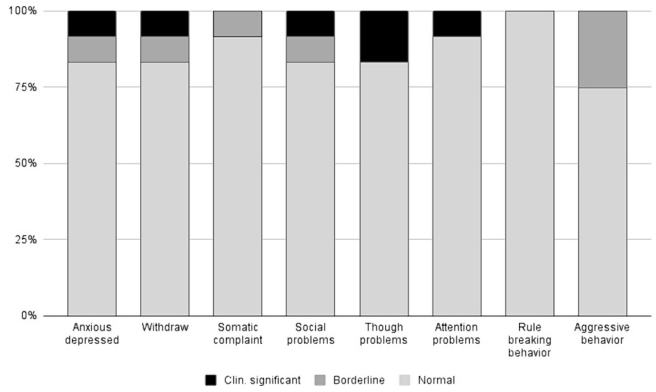

Fig. 2. CBCL 6–18 syndrome scale (administered in 12 cases).
Abbreviation: Clin., clinically.

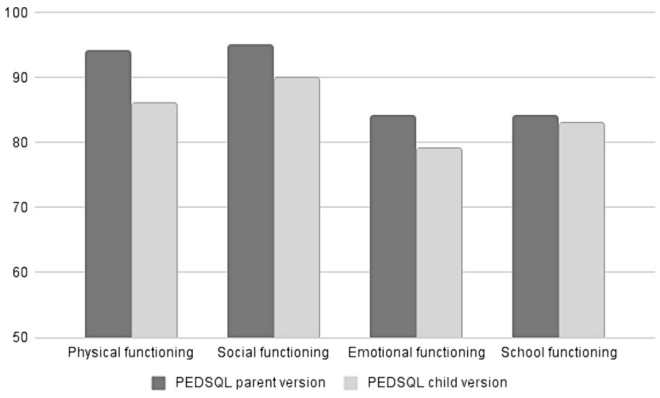

Fig. 3. Mean scores at PEDSQL subscale (administered to 18 parents and 14 children).

Table 3
Scores at SAFA-D and SAFA-S subscales.

	Denial of symptoms (T score < 39)	Normal scores (40 < T < 59)	Borderline scores (60 < T < 69)	Pathological scores (T > 69)
SAFA-A, N (%)	2 (18)	8 (73)	1 (9)	0
Generalized anxiety	1 (9)	10 (91)	0	0
Social anxiety	0	10 (91)	1 (9)	0
Separation anxiety	5 (46)	4 (36)	2 (18)	0
School anxiety	3 (27)	7 (64)	1 (9)	0
SAFA-D, N (%)	1 (9)	10 (91)	0	0
Depression	0	10 (91)	0	1 (9)
Anhedonia	0	9 (82)	2 (18)	0
Irritability	1 (9)	8 (73)	1 (9)	1 (9)
Sense of inadequacy	3 (27)	7 (64)	1 (9)	0
Insecurity	1 (9)	10 (91)	0	0
Sense of guilty	2 (18)	9 (82)	0	0
Hopelessness	0	11 (100)	0	0
SAFA-S, N (%)	4 (36)	6 (55)	0	1 (9)
Somatic symptoms	3 (27)	7 (64)	1 (9)	0
Hypochondria	5 (45)	5 (45)	1 (9)	0

indecision, self-dissatisfaction, and feelings of inferiority. As regards formal structures, the drawing was centered on the sheet in 8 cases (62 %), positioned to the left in 2 (15 %, a sign of immediate emotional expression), and positioned to the right in 3 (23 %, an index of tendency to intellectual control). Ten subjects (77 %) placed the drawing at the bottom, in the lower half of the sheet, indicating insecurity and feelings of being crushed by the environment. The dimensions of the figure were normal for the age only in 1 child (8 %); a smaller drawing, indicative of shyness and fear, was found in 2 children (15 %), while a larger drawing, suggestive of inadequacy with compensatory defenses, in 10 cases (77 %). As for the content level, it is worth noting that nine children (69 %) omitted body features, in particular face features, arms and hands, that could indicate shy personality, difficult or inadequate adaptation and anxiety. The age assigned to the figure was similar to that of the designer in 4 cases (31 %), while the remaining 9 children (69 %) draw a more mature person (adult/elderly) that could be interpreted as an expression of the difficulty of separation-individuation and projection of the ideal self. The gender of the figure was equal to that of the designer (absence of socio-sexual conflicts) in 9 cases (69 %). See Fig. 4 for the most significant drawings.

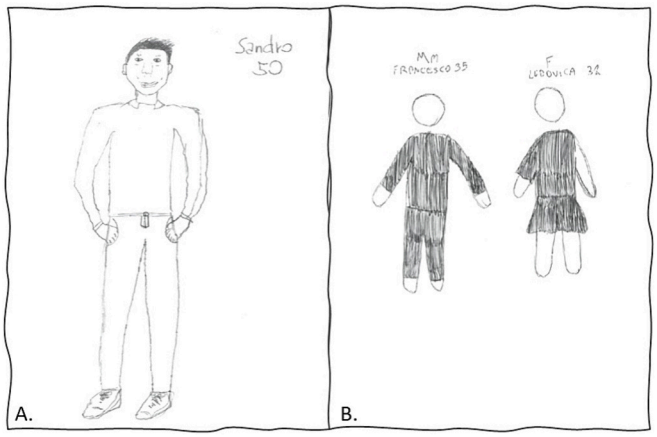

Fig. 4. Drawings at Human Face Drawing Test.
a) Girl, 10 years, 10 months. Sketchy lines, large figure dimension, hands hidden in pocket, opposite gender, defined as older than the author of the drawing.
b) Girl, 11 years, 11 months. Shading and blackening, poor integration of the part of the drawn (head separated from the body), body part omission (all facial features are omitted), absence of hands and feet details, spontaneously drew two figures of both equal and opposite gender and both defined as older than the author of the drawing.

4. Discussion

In the last decades, the improvement in the diagnosis and the management of rheumatic diseases has resulted in an increasing number of successful pregnancies. At the same time, the interest in the long-term development of children has grown, with studies including children born to mothers with systemic lupus erythematosus, rheumatoid arthritis, and antiphospholipid syndrome, and reporting a possible increased risk of neurodevelopmental conditions, such as learning disorders, ASD, attention deficit, speech problems [21–26]. However, to the best of our knowledge, no data are available regarding the neurodevelopmental outcomes of children born to SSc mothers. In the present study, we aimed at detailing the neurodevelopmental/cognitive profile, the adaptive functioning, the quality of life, the behavioral characteristics and the self-image in a sample of children and adolescents born to mothers affected by SSc.

Premature birth was detected in 20 % of cases, which is three-time higher as compared to general population [27] but in line with the increased rate of preterm deliveries already reported in SSc women, ranging from 15 to 25 % [28,29]. Furthermore, we documented a high frequency of cesarean section (55 %), which is also in line with data provided by a recent meta-analysis showing 2–3 folds higher chance of cesarean section for SSc women as compared to controls, mainly driven by Obstetricians' concern about potential disease-related risks [3]. Finally, 60 % of the children (especially those at *very preterm*) presented with perinatal complications. This observation confirms what already reported in literature regarding the association between perinatal complications, prematurity and autoimmune disease [30,31] and the need for hospitalization in neonatal intensive care for their management.

Neurodevelopmental milestones were appropriately acquired by all the sample, as well as communication and language skills, delayed in one child and compromised in another one, who suffered from ASD. These findings are similar to general population (a slow onset and progression of expressive language was reported in 15 % of subjects [32,33], and a developmental language disorder in 5–7 % [34,35]), and to children born to mothers with autoimmune diseases (6 %) [36]. A quarter and almost half of the sample suffered from feeding and sleep disorders, respectively. This prevalence seems to be higher than general pediatric population (10 %) [37] and may suggest an impact of maternal chronic disease on the relationship with child in the first years of life. Physical problems due to the chronic disease (both autoimmune and not) and the correlated emotional distress can interfere with parenthood and baby holding [38], impacting on mother-infant relationship, circadian rhythm, sleep hygiene and the recognition of children' needs and mental health outcome [39]. For this reason, clinicians need to be aware of the possibility of a sleep disorder that determine irritability, diurnal sleepiness, attention and learning difficulties and, thus, affect the overall daily life functioning [40,41].

At the time of direct evaluation, all the children presented with a normal neurological examination, except for the subject with ASD (5 %). This prevalence seems to be higher compared to the general pediatric population (1 %), although to our knowledge no studies are available on the occurrence of ASD in children born to mothers with SSc and the sample size of the present study is relatively small and not enough powered to correctly establish this prevalence. However, the association between ASD and maternal autoimmune disease is still unclear. On one hand, literature reports a potentially increased risk of ASD in infants born to mothers affected by rheumatoid arthritis [23,42,43], systemic lupus erythematosus [44] and antiphospholipid syndrome [45]. Different hypotheses have been raised, including prenatal exposure to

maternal autoantibodies and cytokines [46], which have been shown, in animal models [47], to alter fetal brain development and induce behavioral anomalies in offspring, and to obstetric complications [23,38,44,45,48]. On the other hand, a recent paper by Yin et al. documented the presence of a risk of ASD also in children born to mothers affected by arthralgia, suggesting other pathways of risk than autoimmunity/inflammation [46].

The developmental/cognitive profile was normal in the majority of the sample. The only child with cognitive difficulties suffered from ASD that can justify the low quotients. Our data suggest that intellectual disability represents a rare outcome for children with SSc mothers with a similar prevalence to the general pediatric population (1–3 %) [49]. Normal intelligence levels have been reported also in children born to mothers with systemic lupus erythematosus and antiphospholipid syndrome [22,25,50], leading to the assumption that maternal autoimmunity does not impair offsprings' global intelligence quotient [25,51]. A similar finding concerns the adaptive functioning of our children: in fact, the only child with low score at VABS-II was the ASD patient.

According to the CBCL, 15 % of our children reached the subclinical range for internalizing and/or externalizing problems, and a third of subjects presented with risk score for social and out-of-school activities. This finding, partially confirmed at YSR, may reflect a poor social life and limited extra-school interests. In this regard, children have been described by their mothers with autoimmune rheumatic diseases as "hyper-mature", early independent, behaving as adults, very sensible and responsible, especially towards the mother's needs and worries [38]. Our results could further support these findings, suggesting that a chronic condition may hinder maternal support for the children's social development and emotional-behavioral profile [25,38]. Furthermore, during adolescence maternal illness could be experienced as a limit in the process of gaining autonomy and independence.

None of our children presented with low scores at HRQOL. However, we noticed a discrepancy between parental and children reports, with an overestimation of the data obtained from the parental formats in all the domains, but especially for physical, emotional, social areas. To the best of our knowledge, our study is the first one evaluating the quality of life of children born to mothers affected by rheumatic diseases. We hypothesize that children tend not to fully show their needs and emotions to mothers, which in turn are not able to recognize completely the offspring's difficulties, leading to an overestimation of their psychosocial adaptation.

From the evaluation for psychiatric disturbances, we detected a high risk for anxiety, depressive and somatic disorders. Among all the SAFA-A and -B subscales, the major critical issues emerged for *separation* and *school anxiety*, *anhedonia*, *irritability*, *inadequacy* and *sense of guilty*. These findings could be related to those obtained at CBCL and YSR, as these subjects seem to have a reduced interest in activities commonly considered enjoyable for their age, resulting in poor engagement in out-of-school and social activities. Furthermore, at SAFA-S almost a third of cases had scores compatible with a partial denial of *somatic symptoms* and *hypochondria*. These results, in addition to those emerged from the analysis of the HFDT, seem to confirm the tendency of children to recognize more their mothers' disorders and inconveniences, while denying their own, even if only partially.

The HFDT revealed higher emotional fragility and poor competence in metabolizing one's emotional experiences. Along with immature graphic trait, we detected a higher frequency of body parts omission in children's drawings, especially concerning facial features and hands which are typically deformed in mothers due to SSc. Furthermore, we found that the figure drawn was a mature person (adult/elderly), finding that could reflect how lonely these children may feel when face with a task that regards the processing of anxiety and concerns related to maternal chronic illness, due to their psychic maturity. More in general, the image drawn by the child is a function of the interaction between physical appearance and self-concept or self-esteem. It is therefore conceivable that in these children, the awareness of the maternal illness represented a traumatic event, reinforcing some defenses such as self-holding and leading to hypertrophic development of intellectual abilities and a false-self personality, emotionally fragile.

Regarding potential limitations associated with the study, the relatively small number of patients recruited due to the fact that SSc is a rare disease with a rare onset during reproductive age. Future studies should be conducted in larger samples.

In conclusion, children born to SSc women exhibit normal cognitive and adaptive abilities but an increased vulnerability to psychopathological problems and fragility in social functioning. These observations might reflect, on one hand, that children need to feel adequate and mature to face the task of accepting the chronic disease of their mothers; on the other hand, that the chronic condition of the women may affect children' social, affective and relational development. The early identification of psychopathological and/or social difficulties in the offspring would be worthwhile, in order to help children to overcome their possible difficulties during the developmental years.

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Ethics approval

The study was conducted in accordance with the ethical guidelines set forth by the Declaration of Helsinki and was approved by the Ethical Committee of ASST Spedali Civili in Brescia (NP 5843), Italy.

Consent to participate and publish

Written informed consent was obtained from parents/caregivers of the children, for participating to the study and publishing the results.

CRediT authorship contribution statement

Jessica Galli: Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Erika Loi:** Writing – review & editing, Writing – original draft, Formal analysis. **Maria Grazia Lazzaroni:** Writing – review & editing, Conceptualization. **Anna Molinaro:** Methodology, Data curation. **Laura Andreoli:** Supervision. **Marzia Bendoni:** Data curation. **Liala Moschetti:** Data curation. **Eleonora Pedretti:** Data curation. **Lucrezia Maria Visconti:** Data curation. **Paolo Airò:** Supervision, responsible of Brescia Systemic Sclerosis cohort. **Franco Franceschini:** Supervision. **Angela Tincani:** Writing – review & editing, Supervision, Conceptualization. **Elisa Fazzi:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

Author MGL has received research support from GILS. The other authors declare they have no relevant financial interests.

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