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Mélissa Burgevin: Design of the work, Investigation, Analysis and Interpretation, Writing - Original Draft Preparation, Writing - Review & Editing. **Agnès Lacroix:** Supervision, Critical revision of the article, Funding acquisition. **Karine Bourdet, Régis Coutant, Bruno Donadille, Laurence Faivre, Sylvie Manouvrier-Hanu, Florence Petit, Christel Thauvin-**

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Quality of life and mental health of adolescents and adults with Silver-Russell syndrome

Mélissa Burgevin^{a*}, Agnès Lacroix^a, Karine Bourdet^b, Régis Coutant^c, Bruno Donadille^d,
Laurence Faivre^{e,f}, Sylvie Manouvrier-Hanu^{g,h}, Florence Petitⁱ, Christel Thauvin-Robinet^{e,f},
Annick Toutain^j, Irène Netchine^k, & Sylvie Odent^l

^a Univ Rennes, LP3C (Laboratoire de Psychologie, Cognition, Comportement et Communication), F-35000, Rennes, France

^b Service de Pédiatrie, CHRU Brest, Brest, France

^c Service Endocrinologie Pédiatrique, CHU Angers, Angers, France

^d Endocrinologie, service du Pr Christin-Maitre, Hôpital Saint Antoine, Sorbonne Université, Assistance publique-Hôpitaux de Paris, 75012 Paris, France

^e INSERM – Université de Bourgogne Franche-Comté, UMR 1231 GAD Génétique des Anomalies du Développement, FHU TRANSLAD, CHU Dijon Bourgogne, France

^f CHU Dijon, Centre de référence maladies rares Anomalies du Développement et Syndromes Malformatifs, Centre de Génétique, FHU TRANSLAD, CHU Dijon Bourgogne, France

^g CHU Lille, Centre de référence maladies rares Labellisé pour les Anomalies du Développement Nord-Ouest, Clinique de Génétique, F-59000 Lille, France

^h Univ Lille, EA7364 – RADEME – Maladies Rares du Développement embryonnaire et du Métabolisme : du phénotype au génotype et à la Fonction, F-59000 Lille, France.

ⁱ CHU Lille, Clinique de Génétique Guy Fontaine, F-59000 Lille, France

^j Service de Génétique, Centre Hospitalier Universitaire, UMR 1253, iBrain, Université de Tours, Inserm, Tours, France

^k Sorbonne Université, INSERM UMR_S 938, Centre de Recherche Saint Antoine, APHP, Hôpital Armand Trousseau, Explorations Fonctionnelles Endocriniennes, F-75012, Paris, France

^l Service de Génétique Clinique, Centre Référence Anomalies du Développement CLAD Ouest, Univ Rennes, CNRS, IGDR (Institut de génétique et développement de Rennes), F-35203 Rennes, France

Correspondence concerning this article should be addressed to Mélissa Burgevin, LP3C, Université Rennes 2, Place du Recteur Henri Le Moal, 35043 Rennes, France. E-mail: melissa.burgevin@univ-rennes2.fr

Abstract

Silver-Russell syndrome (SRS) is a rare imprinting disorder characterized by prenatal and postnatal growth retardation. Despite normal intellectual functioning, psychosocial and behavioral difficulties have been observed in this syndrome. However, few studies have dealt with these aspects, even though this could enhance the current understanding of the SRS and, more importantly, improve the management of potential psychosocial problems. Given the sparse literature, this cross-sectional study aimed to establish the psychosocial and behavioral profile of individuals with SRS. To this end, we assessed the quality of life (World Health Organization Quality of Life Questionnaire-Short Form), self-esteem (Coopersmith's Self-Esteem Inventory), anxiety (Spielberger's State-Trait Anxiety Inventory), and behavioral and emotional problems (Child Behavior Checklist and Adult Behavior Checklist) in a sample of 19 adults and adolescents with SRS and 18 without SRS (controls). We also analyzed clinical features, molecular genetic diagnosis, and past or current treatments of participants with SRS. Based on prior studies, we expected to observe psychological and behavioral difficulties in our clinical population. We also expected these difficulties, shared by both adolescents and adults with SRS, to be associated with factors such as height, genetics, or treatment. Overall, our results showed that participants with SRS had similar performances to those of controls, despite high interindividual variability among the adults with SRS. For example, while adults with SRS had a similar mean total self-esteem score to control participants, 45% of the adults with SRS still had very low self-esteem. In addition, adolescents and adults with SRS did not necessarily have the same difficulties. Social and behavioral problems appeared to be more common in adolescents with upd(7)mat while in adults, difficulties were not associated with either height, weight, NH-CSS score, or GH treatment but did appear to be associated with GnRHa treatment. Indeed, low self-esteem was associated with GnRHa treatment. Overall, this study shows that early intervention and multidisciplinary care right up to adulthood,

including psychological support, are needed for this population, regardless of the molecular abnormality responsible for SRS, to cope with potential psychosocial problems.

Keywords: Silver-Russell syndrome, Adolescents, Adults, Self-esteem, Anxiety, Genotype

1. Introduction

Silver-Russell syndrome (SRS; OMIM #180860, also known as Russell-Silver syndrome) is a rare imprinting disorder characterized by prenatal and postnatal growth retardation, facial dysmorphism (mainly relative macrocephaly at birth and protruding forehead), body asymmetry, feeding difficulties, and/or low body mass index in early life (Wakeling et al., 2017). SRS is mainly due to maternal uniparental disomy of chromosome 7 (upd(7)mat) or loss of methylation in the *H19/IGF2* intergenic differentially methylated region of chromosome 11p15 (11p15 LOM). Molecular abnormalities are identified in approximately 60% of patients with SRS (Netchine et al., 2007), but the etiology currently remains unknown for many patients. The diagnosis of SRS is therefore based primarily on clinical observations but can be confirmed by molecular analysis. Currently, the clinical diagnosis relies on the Netchine-Harbison clinical scoring system (NH-CSS; Azzi et al., 2015). This was validated by the International Consensus on the Diagnosis and Management of SRS (Wakeling et al., 2017). In addition to short stature, SRS may be associated with other clinical features, such as maxillofacial anomalies, early puberty, genital anomalies, and metabolic disorders (for a review, see Wakeling et al., 2017). The management of SRS has long been focused on optimizing final height, involving the use of recombinant growth hormone (GH) or a combination of GH and gonadotropin-releasing hormone analogues (GnRHa) in some cases. Today, management is multidisciplinary, early, and specialized for growth, nutrition, gastrointestinal, precocious puberty or premature adrenarche, orthopedic,

maxillofacial, and other problems. Nevertheless, current knowledge of the psychological and behavioral impact of SRS is limited. In a study examining the distress experienced by family caregivers of children with SRS via clinical interviews, families expressed several concerns about aspects of their children's future lives, notably social relationships, potential discrimination, and psychological development (Weng et al., 2012). For example, families fear that their children's physical appearance will negatively impact their self-esteem. In a recent study of the phenotypic characteristics of older patients with SRS, Lokulo-Sodipe et al. (2020) examined life satisfaction, quality of life, and wellbeing in 33 adolescents and adults with genetically confirmed SRS. These different domains were assessed using the Sheehan Disability Scale, the Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW), and the Cantril Scale. Regarding scores on the Sheehan Disability Scale, participants with SRS had a higher score than the general population, reflecting good overall life satisfaction. No difference was found between the scores of participants who had received GH treatment and those who had not. The majority (67%) of participants reported that their symptoms interfered with at least one of the three domains of functioning (e.g., social, family, school/work). Regarding SEIQoL-DW scores, the mean score of participants with SRS was similar to that of healthy adults. No significant correlation was found with participants' standard height score, but there was a negative correlation with standard body-mass index score (BMI), such that SEIQoL scores decreased as BMI increased. Although life satisfaction and quality of life generally appear to be similar to those of the general population, other qualitative studies have found that individuals with SRS encounter psychosocial difficulties. Ballard et al. (2021) recently explored the lived experience of eight adolescents with SRS in clinical interviews. All eight adolescents reported that as early as ten years of age, they experienced psychosocial problems related primarily to feeling and looking different from others. These difficulties were similar to those expressed by 15 adults in

another study using the same interview method (Ballard et al., 2019). In particular, these adults reported experiencing bullying and unpleasant behaviors from strangers (e.g., stares, negative comments) and difficulty forming romantic relationships during adolescence. These problems, as well as concerns about appearance, may lead to anxiety and depressive symptoms in adolescence that sometimes persist in adulthood. Anxiety, depressive symptoms, and behavioral problems have also been identified in case reports of clinical SRS (e.g., Garcia et al., 2012; Karher & Banda, 2017; Plotts & Livermore, 2007). The findings of these studies highlighting psychological and behavioral difficulties in SRS need to be substantiated and confirmed in larger SRS groups to improve current understanding of SRS and, more importantly, to provide more targeted management of potential psychosocial problems.

We therefore investigated the psychosocial and behavioral profiles of adolescents and adults with SRS using psychometric tests. We assessed the quality of life, self-esteem, anxiety, and behavioral difficulties of a cohort of patients with SRS and compared them with healthy controls. We aimed to determine whether 1) the quality of life, self-esteem, anxiety, and behavioral inventory scores of our participants with SRS were poorer than those of controls, and 2) adolescents and adults with SRS had similar difficulties. We also aimed to identify factors potentially associated with the poorer scores of our clinical population.

2. Methods

2.1. Design

We conducted a cross-sectional study between 2016 and 2018. This study formed part of a larger research project regarding the life course and neuropsychological phenotype of SRS (Burgevin et al., 2021). As it involved human participants, the study was reviewed and approved by the ethics committee of Rennes University Hospital, France (no.15.123, 29

December 2015) and was conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent to participate in this research.

2.2. Recruitment and participants

The patients with SRS were recruited via a call for participation in the study. This call was relayed to patients with SRS and their families by geneticists and endocrinologists in various French hospitals, reference centers for developmental anomalies affiliated with the AnDDI-Rares disease healthcare network, and patient support groups.

Participation in this voluntary research was proposed to adolescents and adults who met the following inclusion criteria: 1) SRS confirmed by a molecular diagnosis (upd(7)mat or 11p15 LOM), 2) and aged 13 years or older. Following the call for participation, we talked to 28 potential participants: six people finally refused to participate for different reasons (e.g., lack of time, agreement of the family, but the refusal of the adolescent with SRS), and three people were excluded because of the uncertain molecular basis of their SRS. Therefore, this research involved a total of 19 individuals aged 13-39 years ($M = 20.05$, $SD = 7.21$). The group of adolescents with SRS comprised eight adolescents aged 13-16 years ($M = 14.13$, $SD = 1.25$). Their mean education level was 8.50 years ($SD = 1.07$, range = 7-10), and the mean parental education level was 14.13 years ($SD = 2.03$, range = 10.50-17). The group of adults with SRS comprised 11 adults aged 18-39 years ($M = 24.36$, $SD = 6.64$). Their mean education level was 13.27 years ($SD = 2.15$, range = 9-17), and the mean parental education level was 11.23 years ($SD = 3.24$, range = 5-16).

A control group composed of 18 healthy volunteers aged 13-31 years ($M = 19.06$, $SD = 5.15$) was recruited from the general population through advertising. Controls were matched with patients for age, sex, and education level. None of the controls had SRS, psychiatric or neurodevelopmental disorders, learning disabilities, or other neurological

disorders. None had received GH or GnRHa treatment in their lifetime. The group of adolescents without SRS comprised seven adolescents aged 13-16 years ($M = 14.43$, $SD = 1.13$). Their mean education level was 8.43 years ($SD = 1.13$, range = 7-10), and the mean parental education level was 14.86 years ($SD = 2.93$, range = 10-17). The group of adults without SRS comprised eleven adults aged 18-31 years ($M = 22.00$, $SD = 4.45$). Their mean education level was 13.45 years ($SD = 1.57$, range = 12-17), and the mean parental education level was 12.10 years ($SD = 2.31$, range = 8.50-16).

No differences were observed between the adolescents with SRS and control adolescents on either education level ($U = 26.5$, $p = .899$), or parental education level ($t(13) = 0.57$, $p = .579$). Similarly, no differences were observed between adults with SRS and control adults on either educational level ($t(20) = 0.23$, $p = .823$), or parental education level ($t(19) = 0.70$, $p = .490$). The control adolescents and adults exhibited normal growth parameters at birth and in later life (see Table 1).

Table 1.*Medical characteristics of participants*

| | Adolescents with SRS | Adolescents without SRS | <i>p</i> -value | Adults with SRS | Adults without SRS | <i>p</i> -value | Comparison adolescents vs adults with SRS |
|--|-------------------------|----------------------------|-----------------|---------------------------|-----------------------|-----------------|--|
| Number of patients | 8 | 7 | | 11 | 11 | | |
| Sex (%) | | | | | | | |
| Males | 3 (37%) | 3 (43%) | 1.000 | 7 (64%) | 6 (55%) | 1.000 | 0.370 |
| Females | 5 (63%) | 4 (57%) | | 4 (36%) | 5 (45%) | | |
| Age (in years) | | | | | | | |
| Mean (<i>SD</i>) | 14.13 (1.25) | 14.43 (1.13) | 0.534 | 24.36 (6.64) | 22.00 (4.45) | 0.251 | < 0.001 |
| Range | 13-16 | 13-16 | | 18-39 | 18-31 | | |
| Mean birth parameters (<i>SD</i>) | | | | | | | |
| Gestational age in weeks of amenorrhea | 37.63 (2.33) | 39.71 (1.50) | 0.063 | 37.36 (2.73) | 39.82 (1.17) | 0.013 | 0.829 |
| Weight SDS | -2.79 (1.11) | -0.48 (0.62) | < 0.001 | -3.51 (1.28) | 0.01 (1.16) | < 0.001 | 0.214 |
| Height SDS | -2.89 (1.03) | -0.50 (1.02) | < 0.001 | -3.99 (1.80) | -0.36 (1.22) | < 0.001 | 0.141 |
| Head circumference SDS | -0.66 (1.23) | -0.32 (0.54) | 0.517 | -0.70 (0.76) ^c | 0.36 (1.32) | 0.037 | 0.932 |
| Mean growth parameters at examination (<i>SD</i>) | | | | | | | |
| Weight SDS | -2.50 (1.74) | 0.01 (1.05) | 0.006 | -2.38 (1.63) | -0.29 (0.62) | 0.002 | 0.881 |
| Women Weight SDS | -2.83 (1.69) | 0.04 (0.79) | 0.017 | -3.08 (2.49) | -0.56 (0.79) | 0.067 | 0.860 |
| Men Weight SDS | -1.96 (2.05) | -0.03 (1.55) | 0.263 | -1.98 (0.92) | -0.06 (0.37) | < 0.001 | 0.979 |
| Height SDS | -1.78 (1.22) | -0.18 (1.25) | 0.027 | -2.50 (0.59) | -0.03 (0.93) | < 0.001 | 0.105 |
| Women Height SDS | -2.42 (0.69) | -0.26 (0.70) | 0.002 | -2.71 (0.55) | -0.60 (1.03) | 0.008 | 0.512 |
| Men Height SDS | -0.71 (1.24) | -0.09 (1.98) | 0.670 | -2.37 (0.62) | 0.45 (0.54) | < 0.001 | 0.018 |
| Molecular genetic diagnosis (%) | | | | | | | |
| 11p15 LOM | 5 (63%) | | | 11 (100%) | | | 0.058 |
| upd(7)mat | 3 (37%) | | | 0 (0%) | | | |
| NH-CSS clinical diagnosis | | | | | | | |
| Total score (median, <i>IQR</i>) | 5.5 (5-6) | | | 6 (5-6) ^b | | | 0.890 |

| | | | |
|---------------------------------------|------------|---------------------------|-------|
| <i>Number of items (%)</i> | | | |
| Small for gestational age | 8/8 (100%) | 11/11 (100%) | |
| Postnatal growth features | 7/8 (88%) | 9/10 ^b (90%) | 1.000 |
| Relative macrocephaly at birth | 7/8 (88%) | 10/10 ^b (100%) | 0.421 |
| Protruding forehead | 8/8 (100%) | 9/9 ^b (100%) | |
| Body asymmetry | 5/8 (63%) | 10/10 ^b (100%) | 0.275 |
| Feeding difficulties | 8/8 (100%) | 11/11 (100%) | |
| Past/current treatments (%) | | | |
| Growth hormone treatment | 7 (88%) | 7 (64%) | 0.338 |
| Gonadotropin-releasing hormone analog | 8 (100%) | 6 (55%) | 0.045 |

Note. SRS = Silver-Russell syndrome; Adolescents aged < 18 years; Adults aged ≥ 18 years; SD = standard deviation; SDS = standard score or z-score; 11p15 LOM = loss of methylation on chromosome 11p15; upd(7)mat = maternal uniparental disomy of chromosome 7; NH-CSS = the Netchine-Harbison Clinical Scoring System; IQR = interquartile range. ^a Analyses were performed using Fisher's exact tests for categorical variables, *t*-tests for continuous variables with normal distribution, and Mann-Whitney *U*-tests for continuous variables with non-normal distribution. ^b Several items of the NH-CSS items could not be assessed in adults. ^c For head circumference, *n* = 10 for the adults group.

2.3. Procedure

Each participant was interviewed at home as part of a larger research project (Burgevin et al., 2021). Psychological and behavioral data were collected from the participants/parents using questionnaires completed in their homes. Once completed, the questionnaires were to be returned to the examiner by mail within a maximum of one to two months. A written report of the results was sent to each participant, including recommendations when the participant had clinically significant scores. Telephone feedback was also offered in addition to the written report. Medical and clinical data were collected from the medical records of participants with SRS and during a clinical examination by an endocrinologist or geneticist.

2.4. Medical and clinical information

Neonatal parameters (height, weight, and head circumference at birth), height and weight, molecular genetic diagnosis, NH-CSS clinical score, and current and past treatment were collected. The NH-CSS comprises six items: 1) born small for gestational age (birth weight and/or birth length ≤ -2 standard deviation score, SDS); 2) postnatal growth retardation (height ≤ -2 SDS at 24 months or height ≤ -2 SDS below midparental target height); 3) relative macrocephaly at birth (head circumference at birth ≥ 1.5 SDS above birth weight and/or length SDS); 4) protruding forehead at 1–3 years; 5) feeding difficulties and/or low BMI (BMI ≤ -2 SDS at 24 months) in early life; 6) body asymmetry (Azzi et al., 2015; Wakeling et al., 2017).

2.5. Psychological and behavioral measures

Participants' quality of life was assessed using the validated French version of the World Health Organization Quality of Life Questionnaire-Short Form (WHOQOL-BREF;

WHOQOL Group, 1998), a cross-cultural instrument developed by the World Health Organization. This self-reported questionnaire measures subjectively perceived quality of life in patients with physical or mental disorders and healthy individuals. It contains 26 items, including two concerning overall satisfaction with health and overall perception of quality of life. The remaining 24 assess quality of life in four specific domains: physical health (e.g., activities of daily living, physical pain and discomfort, dependence on medical treatment and aids, energy and fatigue), psychological health (e.g., body image and appearance, negative and positive feelings, learning and concentration), social relationships (e.g., personal relationships, social support, sexual activity), and environment (e.g., financial resources, home environment, leisure activities, transport). We considered these four domains and the two items that address overall health satisfaction and overall perceived quality of life. For each domain, scores range from 0 to 100, with higher scores indicating better quality of life. For each item, scores range from 1 to 5, with higher scores indicating better perceived quality of life and better satisfaction with health.

The French version of the Coopersmith's Self-Esteem Inventory (CSEI; Coopersmith, 1984) was used to evaluate self-esteem. The CSEI consists of 58 sentences expressing feelings, opinions, and reactions typical of various everyday situations. For each sentence, participants have to indicate whether or not it describes their usual way of thinking or acting ("Like me" vs "Unlike me"). The CSEI consists of a general subscale (26 items) and three additional subscales (8 items for each) assessing self-esteem in the social, family, and academic/professional domains. The sum of the four subscales constitutes the total CSEI score, ranging from 0 to 50. A score of 33 for adults (18 for adolescents) is regarded as the threshold below which self-esteem is abnormally low. The CSEI also includes an 8-item *lie* subscale that is not included in the total CSEI score. A high score on this scale may indicate

defensiveness when performing the test or a clear desire to make oneself look good (Coopersmith, 1984).

The French version of the Spielberger's State-Trait Anxiety Inventory (STAI Y form; Spielberger et al., 1993) assessed anxiety. This self-administered questionnaire consists of two 20-item subscales: the STAI-A assesses state anxiety, which corresponds to the actual level of anxiety at the time of the assessment; the STAI-B assesses trait anxiety, which corresponds to a personality trait (i.e., usual, general, and stable anxiety). The raw scores are transformed into T-scores, with higher scores indicating greater anxiety. A T-score above 55 is considered abnormally high according to French norms.

The Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) and Adult Behavior Checklist (ABCL; Achenbach, 2003) parental report questionnaires were used to evaluate behavioral and emotional problems during the preceding six months in adolescents (< 18 years) and adults (\geq 18 years). These CBCL contains 113 items, divided into eight syndrome subscales: Anxious/Depressed, Withdrawn/Depressed, Somatic complaints, Social problems, Thought problems, Attention problems, Rule-breaking behavior, and Aggressive behavior. The ABCL contains 134 items, again divided into eight syndrome subscales: Anxious/Depressed, Withdrawn, Somatic complaints, Thought problems, Attention problems, Aggressive behavior, Rule-breaking behavior, and Intrusive. The CBCL and ABCL both yield a total problems score and internalizing and externalizing problems scores. All the syndrome subscores and the total score, internalizing, and externalizing scores were converted to age- and sex-adjusted T-scores. Higher scores indicated an increased risk of psychopathology.

2.6. Statistical analyses

Z-scores for neonatal parameters, height, and weight were calculated using PediTools electronic growth chart calculators (Chou et al., 2020; <http://peditools.org/fenton2013>).

Statistical analyses were performed using Jamovi (version 1.6.23.0; The jamovi project, 2021). Descriptive statistics were used to describe the characteristics of the adolescents and adults SRS groups. Normality of distributions was assessed with the Shapiro-Wilk normality test and confirmed by inspection of the Q-Q plot. Independent *t*-tests and Welch's *t*-test were used to compare the two groups for continuous variables with a normal distribution. Mann-Whitney *U*-tests were used for continuous variables with non-normal distribution. For effect sizes, we calculated and interpreted Cohen's *d* for the independent *t*-tests and Welch's *t*-test and rank-biserial correlations (r_{rb}) for the Mann-Whitney *U*-tests. Fisher's exact test was used for categorical variables. To explore the relationships between psychological and behavioral scores (e.g., total self-esteem score) and medical characteristics (e.g., height, weight, and NH-CSS score), we used Pearson correlations (*r*) for variables with a normal distribution and Spearman correlations (ρ) for variables with a non-normal distribution. Analyses of variance (ANOVAs) were used to determine the effect of treatment (GH or GnRHa) and the interaction effect between treatments on questionnaire scores.

3. Results

3.1. Clinical characteristics of participants with SRS

The clinical and medical features of adolescents and adults with SRS are shown in Table 1. Virtually all (95%) participants had an NH-CSS score of 4 or above. A difference of borderline significance was observed on the median NH-CSS score between adolescents with mUDP7 (*Mdn* = 5; IQR = 4.5-5) and adolescents with 11p15 LOM (*Mdn* = 6; IQR = 6-6), $U = 1.00$, $p = .050$, $r_{rb} = 0.87$, large effect size. According to the literature (e.g., Wakeling et al., 2010; Wakeling et al., 2017), this trend suggests a link between phenotype and genotype. Participants in our research were born between 31 and 41 weeks of amenorrhea ($M = 37.47$; $SD = 2.50$). Four participants were born preterm: three were born between 32 and 36 weeks

(moderate to late preterm), and one was born very preterm (31 weeks). However, for three of these participants, prematurity occurred in the context of a twin pregnancy in the 11p15 LOM subgroups (one in the adolescent subgroup and two in the adult subgroup).

Height, weight, and head circumference at birth were equivalent in adolescents and adults with SRS. No significant differences were observed on mean SDS height, $t(2.33) = 0.08$, $p = .946$, between adolescents with 11p15 LOM ($n = 5$; $M = -1.74$, $SD = 0.74$) and adolescents with upd(7)mat ($n = 3$; $M = -1.83$, $SD = 2.03$). The girls with 11p15 LOM ($n = 3$) had a mean height SDS of -2.03 ($SD = 0.61$; range = -2.72 to -1.58) and the girls with upd(7)mat ($n = 2$) had a mean height SDS of -3.00 ($SD = 0.20$; range = -3.14 to -2.86). The boys with 11p15 LOM ($n = 2$) had a mean height SDS of -1.31 ($SD = 0.93$; range = -1.97 to -0.66) and the boy with upd(7)mat had a height SDS of 0.50 .

Their mean final height SDS of adults with 11p15 LOM was -2.50 ($SD = 0.59$; range = -3.27 to -1.30). The majority (82%) had a height SDS below -2 SDS. The mean final height SDS of adults who had received GH treatment ($n = 7$) was -2.72 ($SD = 0.38$; range = -3.27 to -2.2): -2.85 ($SD = 0.57$; range = -3.27 to -2.2) for the women ($n = 3$) and -2.63 ($SD = 0.20$; range = -2.82 to -2.35) for the men ($n = 4$). The mean final height SDS of adults who had received both GH and GnRHa treatments ($n = 5$) was -2.54 ($SD = 0.26$; range = -2.82 to -2.2): -2.63 ($n = 4$; $SD = 0.17$; range = -2.82 to -2.35) for the men and -2.2 for the woman.

3.2. Psychosocial and behavioral profiles

3.2.1. Self-esteem and anxiety

On the CSEI, the adolescents with SRS ($M = 41.88$, $SD = 5.94$) and control adolescents ($M = 37.86$, $SD = 5.96$) did not differ on the total score, $t(13) = 1.31$, $p = .214$. Descriptive statistics showed that the mean score on the social subscale ($M = 6.38$, $SD = 1.41$)

was lower than the mean score on either the family subscale ($M = 7.63$, $SD = 0.52$) or the academic subscale ($M = 6.88$, $SD = 1.25$) in adolescents with SRS. The Mann-Whitney test did not reveal any significant difference between adolescents with SRS ($M = 3.13$, $SD = 0.83$) and control adolescents ($M = 2.29$, $SD = 2.06$) on the lie subscore, $U = 22$, $p = .513$. For adolescents with SRS, the total self-esteem score was correlated with neither height, $r(8) = -.05$, $p = .912$, nor weight, $\rho(8) = -.29$, $p = .501$. Surprisingly, a positive correlation was observed between the total self-esteem score and the NH-CSS score, $\rho(8) = .72$, $p = .045$. A significant difference was also found between adolescents with 11p15 LOM ($n = 5$; $M = 45.60$, $SD = 3.21$) and adolescents with upd(7)mat ($n = 3$; $M = 35.67$, $SD = 3.21$), $t(6) = 4.24$, $p = .005$, $d = 3.09$ (large effect size).

Descriptive statistics showed that adults with SRS ($n = 11$; $M = 36.73$, $SD = 7.42$) had a lower mean total self-esteem score than control adults ($n = 10$; $M = 39.80$, $SD = 7.27$). However, this difference was not significant, $t(19) = 0.96$, $p = .351$. Five adults with SRS (45%) nevertheless had a total self-esteem score of 33 or less, indicating very low self-esteem. As with the adolescents with SRS, descriptive statistics showed that the mean score on the social subscale ($M = 5.82$, $SD = 1.17$) was lower than the mean scores on the family ($M = 6.73$, $SD = 1.85$) and professional ($M = 6.45$, $SD = 1.69$) subscales in adults with SRS. A difference of borderline significance was observed between adults with SRS ($M = 3.18$, $SD = 1.60$) and control adults ($M = 1.90$, $SD = 1.20$) on the lie subscore, $t(19) = 2.06$, $p = .053$, $d = 0.90$ (large effect size). Several adults with SRS responded unusually well to items on the lie subscale. For example, they responded “like me” to the items “I always tell the truth”, “I always do the right thing”, “I like everyone I know”, “I always know what to say to people”. These responses may reflect these participants’ conscious or unconscious desire to give a good account of themselves (social desirability bias). Therefore, adults with high scores on this lie subscale may have lower self-esteem than reported. For adults with SRS, the

total self-esteem score was not correlated with either height, $r(11) = .12, p = .718$, weight, $r(11) = -.27, p = .429$, or NH-CSS score, $\rho(11) = -.27, p = .423$. However, there was a difference in the mean total self-esteem score between adults who had received GnRHa treatment ($n = 6; M = 41.83, SD = 4.88$) and those who had not ($n = 5; M = 30.60, SD = 4.67$), $F(3, 7) = 13.49, p = .008, \eta_p^2 = 0.66$ (large effect size). Adults who had not received GH treatment had a lower mean total self-esteem score ($n = 4; M = 32.25, SD = 8.96$) than those who had ($n = 7; M = 39.29, SD = 5.53$). However, this difference was not significant, $F(3, 7) = 0.18, p = .688$. The interaction between GH and GnRHa was not significant, $F(3, 7) = 2.55, p = .154$.

Regarding STAI scores, no difference was observed between adolescents with SRS ($M = 39.63, SD = 5.10$) and control adolescents ($M = 42.86, SD = 6.89$) on state anxiety, $t(13) = 1.04, p = .316$, but a difference was observed on trait anxiety, $t(13) = 3.23, p = .007, d = 1.67$ (large effect size). Adolescents with SRS ($M = 31.75, SD = 6.56$) had a lower mean trait anxiety score than control adolescents ($M = 42.57, SD = 6.37$), indicating that they were less anxious than their peers. No difference was observed between adults with SRS ($M = 50.73, SD = 11.26; M = 46.09, SD = 11.38$) and control adults ($M = 46.27, SD = 4.71; M = 46.55, SD = 7.53$) on either state, $t(13.40) = 1.21, p = .247$, or trait, $t(20) = 0.11, p = .913$, anxiety. However, two adults with SRS had high trait anxiety scores.

3.2.2. Quality of life

The adolescents with SRS and control adolescents did not differ on any of the WHOQOL-BREF domains and items (see Table 2), except for satisfaction with health, $t(13) = 2.71, p = .018, d = 1.40$ (large effect size). The overall health satisfaction score was not correlated with either height, $r(8) = .27, p = .524$, weight, $\rho(8) = .33, p = .429$, or NH-CSS score, $\rho(8) = .12, p = .778$. There were no significant differences between adolescents with

11p15 LOM ($M = 3.60$, $SD = 0.55$) and adolescents with upd(7)mat ($M = 3.33$, $SD = 0.58$), $t(6) = 0.65$, $p = .537$.

Table 2.

Comparison of WHOQOL-BREF scores for adolescent and adult participants with SRS and controls.

| Mean (SD) | Adolescents with SRS ($n = 8$) | Adolescents without SRS ($n = 7$) | p-value ^a | Adults with SRS ($n = 11$) | Adults without SRS ($n = 11$) | p-value ^a |
|--|----------------------------------|-------------------------------------|----------------------|------------------------------|---------------------------------|----------------------|
| Physical health | 84.63 (13.15) | 85.86 (13.31) | 0.860 | 80.82 (8.15) | 79.64 (11.68) | 0.786 |
| Psychological health | 78.13 (14.21) | 65.29 (18.89) | 0.157 | 62.82 (18.29) | 70.64 (11.00) | 0.239 |
| Social relationships | 75.00 (15.88) | 72.29 (17.20) | 0.756 | 62.55 (10.17) | 76.91 (12.16) | 0.007 |
| Environment | 91.50 (9.44) | 86.86 (16.41) | 0.506 | 77.36 (15.93) | 77.45 (13.55) | 0.989 |
| Item 1 : overall perception of quality of life | 4.63 (0.52) | 4.29 (0.76) | 0.323 | 4.18 (0.40) | 4.18 (0.60) | 0.966 |
| Item 2 : overall satisfaction with health | 3.50 (0.53) | 4.43 (0.79) | 0.018 | 3.73 (0.90) | 3.82 (0.87) | 0.804 |

Note. SD = standard deviation; SRS = Silver-Russell syndrome; SD = standard deviation; ^a Analyses were performed using *t*-tests for continuous variables with normal distribution, and Mann-Whitney *U*-tests for continuous variables with non-normal distribution.

For adults with SRS, the social relationships subscore was correlated with neither height, $\rho(11) = .27$, $p = .424$, weight, $\rho(11) = -.38$, $p = .254$, nor NH-CSS score, $\rho(11) = -.22$, $p = .506$. A difference of borderline significance was observed between adults who had received GnRHa treatment ($n = 6$; $M = 67.83$, $SD = 9.22$) and those who had not

($n = 5$; $M = 56.20$, $SD = 7.76$), $F(3,7) = 4.72$, $p = .066$, $\eta_p^2 = 0.40$ (large effect size) on the mean social relationships subscore. No significant difference was observed between the adults who had not received GH treatment ($n = 4$; $M = 59.25$, $SD = 10.87$) and those who had ($n = 7$; $M = 64.43$, $SD = 10.10$), $F(3, 7) = 0.06$, $p = .816$. The interaction between GH and GnRH α was non-significant, $F(3, 7) = 1.21$, $p = .309$. Moreover, the social relationships subscore was positively correlated with the total self-esteem score, $\rho(11) = .62$, $p = .044$.

3.2.3. Behavioral and emotional problems

Table 3 shows the mean scores on the CBCL subscales for the two groups of adolescents. For the thought problems subscale and the others, the mean scores of adolescents with SRS were not clinically significant (scores < 65) according to the test manual (Achenbach & Rescorla, 2001). For adolescents with SRS, the thought problems subscore was not correlated with neither height, $r(8) = .19$, $p = .655$, nor weight, $\rho(8) = .42$, $p = .301$. A correlation between the thought problems subscore and the NH-CSS score suggested that the two were negatively associated. However, this correlation was not significant, $\rho(8) = -.64$, $p = .086$. Welch's t -test indicated that adolescents with 11p15 LOM ($n = 5$; $M = 55.60$, $SD = 7.13$) had a lower mean thought problems subscore than adolescents with upd(7)mat ($n = 3$; $M = 66.67$, $SD = 2.52$), $t(5.37) = 3.16$, $p = 0.023$, $d = 2.07$ (large effect size). At the individual level, four adolescents with SRS had borderline clinical scores (65-69) for somatic complaints, social problems, thought problems, and/or attention problems. One these four teenagers had a Withdrawn/Depressed subscore within the clinical range (≥ 70).

Table 3.

Comparison of CBCL scores for age subgroups of adolescents with SRS and controls.

| Mean (SD) | Adolescents with SRS (<i>n</i> = 8) | Adolescents without SRS (<i>n</i> = 7) | p-value ^a |
|----------------------------|---|--|----------------------|
| CBCL subscales | | | |
| Anxious/Depressed | 51.88 (3.40) | 52.57 (3.82) | 1.000 |
| Withdrawn | 55.25 (6.78) | 53.43 (3.26) | 0.906 |
| Somatic complaints | 56.75 (7.15) | 53.43 (6.80) | 0.314 |
| Social problems | 54.00 (6.55) | 52.71 (4.11) | 0.668 |
| Thought problems | 59.75 (7.98) | 51.86 (2.85) | 0.028 |
| Attention problems | 54.63 (5.73) | 51.14 (1.95) | 0.127 |
| Rule-breaking behavior | 53.13 (4.55) | 52.14 (4.38) | 0.165 |
| Aggressive behavior | 51.50 (2.39) | 52.14 (3.39) | 0.950 |
| CBCL Total problems | 50.38 (8.07) | 44.14 (9.67) | 0.144 |
| CBCL Internalizing | 51.00 (9.32) | 47.71 (10.37) | 0.529 |
| CBCL Externalizing | 49.13 (5.19) | 44.86 (10.99) | 0.343 |

Note. SD = standard deviation; SRS = Silver-Russell syndrome. ^a Analyses were performed using *t*-tests or Welch's *t*-test for continuous variables with normal distribution, and Mann-Whitney *U*-tests for continuous variables with non-normal distribution.

Adults with SRS did not differ on the different ABCL subscales (see Table 4). As before, mean subscores were not clinically significant (scores < 65) according to the test manual (Achenbach, 2003). However, at the individual level, four adults with SRS had borderline clinical or pathological scores. For example, two adults had clinical scores on the Anxious/Depressed subscale, and one had a borderline clinical score on this subscale.

Table 4.

Comparison of ABCL scores for age subgroups of adults with SRS and controls.

| Mean (SD) | Adults with SRS (<i>n</i> = 11) | Adults without SRS (<i>n</i> = 10) | p-value ^a |
|----------------------------|-------------------------------------|--|----------------------|
| ABCL subscales | | | |
| Anxious/Depressed | 58.09 (8.28) | 55.70 (7.29) | 0.392 |
| Withdrawn | 58.64 (5.30) | 55.00 (4.22) | 0.100 |
| Somatic complaints | 57.36 (7.65) | 52.80 (4.61) | 0.150 |
| Thought problems | 52.82 (4.62) | 53.90 (4.84) | 0.610 |
| Attention problems | 57.91 (4.04) | 54.90 (4.68) | 0.130 |
| Aggressive behavior | 54.18 (4.85) | 54.10 (4.36) | 0.971 |
| Rule-breaking behavior | 52.82 (3.49) | 55.80 (4.39) | 0.100 |
| Intrusive | 56.73 (7.43) | 57.80 (3.16) | 0.321 |
| ABCL Total problems | 54.00 (7.55) | 52.50 (5.42) | 0.273 |
| ABCL Internalizing | 57.73 (9.41) | 51.70 (10.61) | 0.184 |
| ABCL Externalizing | 51.09 (9.59) | 54.60 (5.02) | 0.314 |

Note. SD = standard deviation; SRS = Silver-Russell syndrome. ^a Analyses were performed using *t*-tests or Welch's *t*-test for continuous variables with normal distribution, and Mann-Whitney *U*-tests for continuous variables with non-normal distribution.

4. Discussion

Previous studies have shown that individuals with SRS can have psychosocial and behavioral difficulties (e.g., Ballard et al., 2019, 2021; Garcia et al., 2012; Karher & Banda, 2017; Plotts & Livermore, 2007). The objective of the present study was to confirm these observations and explore factors that may be associated with these difficulties.

Contrary to our assumptions, WHOQOL-BREF, CSEI, STAI, and CBCL/ABCL scores showed that adolescents and adults with SRS overall had similar scores to controls. Adolescents and adults with SRS exhibited different difficulties. Regarding the WHOQOL-BREF, scores on the item concerning the perceived quality of life showed that adolescents and adults with SRS felt they had a good or very good quality of life. This result is similar to

a previous study of a cohort of adolescents and adults (Lokulo-Sodipe et al., 2020). In terms of satisfaction with their health, adolescents with SRS had lower satisfaction than their peers of the same age. Teenagers with SRS still have to undergo many treatments, such as GH and/or GnRHa, orthodontic treatments, and even gastrostomy, which may give them a different perception of their health. No such difference was observed between the adult groups. However, adults with SRS reported a lower quality of life in social relationships than control adults. This result is consistent with the finding of a recent study in which adults reported difficulties forming social relationships, and more specifically, romantic relationships (Ballard et al., 2019).

A difference on the CBCL thought problems subscore was also observed between the adolescent groups but not between the adult groups. Adolescents with SRS had higher scores than control adolescents, including difficulties with obsessive thoughts or picking parts of the body. Interestingly, the higher this subscore, the lower the NH-CSS score. Thus, it is not surprising that adolescents with *upd(7)mat* had a higher score on this subscale than adolescents with *11p15 LOM*. Individuals with *upd(7)mat* typically have lower NH-CSS scores, as they have a less frequently with the clinical features of SRS (e.g., they tend to have greater birth height and weight, and no asymmetry) than those with *11p15 LOM* (Azzi et al., 2015; Wakeling et al., 2017). However, they have more frequently exhibit neurocognitive and behavioral disorders (e.g., Lane et al., 2020; Wakeling et al., 2010). Our results are consistent with this, as the adolescents with *upd(7)mat* in our group seemed to be emotionally and behaviorally less robust (e.g., thought problems, less self-confidence). In the light of these results, it seems necessary to offer appropriate care and support to these adolescents. In addition to the syndrome's characteristics, the associated cognitive and behavioral difficulties may weaken their self-esteem. Psychological support may therefore be all the more necessary for adolescents with this molecular anomaly.

While it seems important to be alert to the psychosocial difficulties that adolescents with upd(7)mat may experience, individuals with 11p15 LOM should not be overlooked. Although no difference was found between the adult groups, except for the quality of life in social relationships, considerable interindividual variability was observed in adults with 11p15 LOM. Several adults with 11p15 LOM had low self-esteem, high trait anxiety, or clinical scores on the ABCL Anxious/Depressed subscale. The psychosocial difficulties experienced by these individuals may have emerged in adulthood but may also have dated from childhood or adolescence and become more pronounced in adulthood. Most of these adults did not receive early multidisciplinary care (including psychological support) during childhood or adolescence. They generally ceased to benefit from medical follow-up once they reached adulthood, as this support generally stopped when GH treatment came to an end. As Ballard et al. (2019) point out, adults may therefore experience difficulties when specialist care ceases. Our results underscore the importance of psychosocial assessment and psychological support at different life stages (childhood, adolescence, adulthood), and support during the transition from pediatric to adult services, to limit or manage potential psychosocial difficulties. Multidisciplinary management thus seems essential to prevent or manage psychosocial problems and other health problems (both clinical and research) such as orthopedic, metabolic, or reproductive problems in adulthood. If this is not already the case, it may be appropriate to refer adults to patient support groups.

Regarding the factors associated with our results, the height and weight of participants with SRS were not associated with their psychosocial scores. Lokulo-Sodipe et al. (2020) reported the same results regarding height, weight, and data related to life satisfaction, disability, and quality of life. These results are not surprising. Indeed, several studies have pointed out that psychosocial problems are not a straightforward way to the severity of visible difference (such as height, weight, or some of the NH-CSS criteria in our study) (Robinson,

1997; Rumsey et al., 2004). The experience of visible difference is subjective and multi-factorial: it depends on the characteristics of visible difference, but also the individual's developmental stage, and the personal (e.g., personality, coping strategies), social (e.g., family environment, social support), and contextual (e.g., cultural factors) characteristics (Pruzinsky, 2004; Rumsey & Harcourt, 2004, 2007). The severity of visible differences in the SRS (e.g., small stature or presence of asymmetry) should not be the basis of identifying people at risk of psychosocial difficulties. A systematic assessment of psychosocial problems should be carried out in all individuals living with SRS.

Like Lokulo-Sodipe et al. (2020), we also failed to observe a difference between adults who had received GH treatment and those who had not on the different variables. GnRHa treatment unexpectedly had a greater effect. Children with SRS may begin central puberty at a relatively early age, which can be delayed or slowed by GnRHa treatment. Its use in combination with GH treatment is recommended in some cases to increase the growth potential of children with SRS (e.g., Smeets et al., 2016; Wakeling et al., 2017). In our study, the total self-esteem score did not seem to be influenced by the combination of GH and GnRHa-only by GnRHa treatment. Adults who had received GnRHa treatment had higher self-esteem than those who had not. One possible explanation is that going through early puberty in childhood/adolescence may weaken self-esteem. Several studies have suggested that adolescents with central precocious puberty or early puberty (without SRS) experience social and behavioral problems (for a review, see Williams et al., 2018). The feeling of being different that was reported by adolescents with SRS in Ballard et al. (2021)'s study may be reinforced by the bodily changes inherent to puberty. However, to support and confirm this hypothesis, we would have needed to collect the age at onset of pubertal signs in our adults with SRS. Although further studies are needed to confirm this result, it is still an original contribution to the literature.

This study has several limitations. The first major limitation is the small number of participants with and without SRS. Studies with larger cohorts are needed to draw more robust conclusions and explore deeper the large interindividual variability. Moreover, our analyses concerning the relationship between phenotype and genotype could only be performed in groups of adolescents with SRS because we could not recruit adults with *upd(7)mat*. Future studies should try to include more participants with this molecular anomaly. The second limitation of this study is the potential existence of a volunteer bias in the recruitment of cohorts. Indeed, when the sample consists of volunteers, the risk is that they are not representative of the general population with SRS. For example, participants and families with a relatively stable social environment, high quality of life, and high self-esteem may have been more likely to agree to participate in this study than other patients. Another limitation relates to the cross-sectional study design. A longitudinal study would have allowed us to provide a causal interpretation of the observed associations and better understand the difficulties encountered by the clinical population. In addition, tomorrow's adolescents and adults may exhibit different difficulties from those exhibited by the adolescents and adults in the present study, insofar as the management of the syndrome has improved considerably in recent years, as knowledge about SRS has increased, and a consensus on its management has established (Wakeling et al., 2017). In this study, adolescents and adults did not already appear to have received the same management: adolescents did appear to receive early multidisciplinary care. Therefore, it would be interesting to launch a longitudinal study tracking children and adolescents up to adulthood. Currently, children may receive better management than the adolescents of our group (e.g., optimization of the duration of treatments, psychological care). Finally, to better study the effect of treatments on the psychosocial profile of participants, it would be interesting to consider the age of onset and

duration of treatments. These may have differed between the adolescents and adults in our study.

In summary, this study confirmed previous research regarding the reported psychosocial problems in adolescents and adults living with SRS by comparing them to groups of matched control and using objective measures. While the study did not discover significant differences between the groups, clinically significant scores were observed in the SRS group: adults reported a lower quality of life in the social relationship than controls, and adolescents with SRS had higher incidents of obsessive thinking. In addition, several adults had low self-esteem and high trait anxiety. A phenotype-genotype association was also observed for social and behavioral problems, such that adolescents with $\text{upd}(7)\text{mat}$ had more problems than adolescents with $11\text{p}15\text{ LOM}$. In adults, the low self-esteem scores were not associated with either height, weight, NH-CSS score, or GH treatment, although they did appear to be associated with GnRHa treatment. Early intervention and multidisciplinary care (including psychological support) throughout the life span are needed for this population. A routine assessment of psychosocial issues at different life stages is essential for all people living with SRS (regardless of the severity of the SRS or the molecular genetic diagnosis).

Ethics approval and consent to participate

This study involving human participants was reviewed and approved by the ethics committee of Rennes University Hospital, France (no. 15.123, 29 December 2015). It was also conducted in accordance with the Declaration of Helsinki. All participants (and their parents in the case of adolescents) provided their written informed consent to participate in this study.

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Declaration of competing interests

The authors declare that they have no competing interests.

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