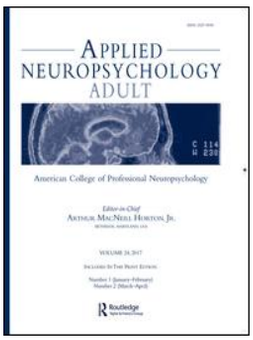

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Intellectual functioning in Silver-Russell syndrome: First study in adults

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ABSTRACT

Silver-Russell syndrome (SRS) is a rare genetic disorder (estimated incidence 1/30,000 to 100,000 live births). So far, only a few studies have focused on the cognitive profile of individuals with SRS, and these were conducted some time ago, concentrated on pediatric cohorts, and included patients who had been diagnosed using a variety of clinical diagnostic systems. There has yet to be any research on the intellectual functioning of adults with SRS. This study sought to establish the intelligence, strengths and weaknesses within intellectual profile of adults with SRS, compared with normative data. Ten individuals with 11p15 epimutation aged 18–39 years completed the Wechsler Adult Intelligence Scale-Fourth Edition. Measures of interest included participants' intelligence (Full Scale Intelligence Quotient [FSIQ]) and four domains of cognitive functioning: verbal comprehension, perceptual reasoning, working memory and processing speed. Discrepancy scores were calculated, and descriptive statistical and linear correlations were used to investigate factors associated with IQ outcome. Clinical and medical information such as rehabilitation, and perceived difficulties in daily life were collected by interviews and questionnaires. Results showed that the mean FSIQ score was in the average range ($M = 95.40$, $SD = 18.55$) and they performed best on verbal comprehension. Frequent daily difficulties were reported by patients and/or their families: learning disabilities and low self-esteem were perceived by 60% of adults. Early intervention and multidisciplinary care from childhood to adulthood are important in SRS for care potential medical, cognitive and psychosocial problems. This is the first study to document the intellectual functioning of adults with SRS.

KEYWORDS

11p15 Epimutation; adults; cognitive profile; intellectual assessment; Silver-Russell syndrome

Introduction

Silver-Russell syndrome (SRS, OMIM #180860) is a rare genetic disorder with an estimated incidence of between 1 in 30,000 and 1 in 100,000 live births worldwide (Wakeling et al., 2017). In Estonia, a retrospective study found the birth prevalence of SRS with known molecular abnormalities to be 1 in 54,537 (Yakoreva et al., 2015). The exact frequency of this syndrome is currently unknown. Furthermore, it is clinically and genetically heterogeneous. Concerning the genetics, two main molecular mechanisms have been identified in SRS: a maternal uniparental disomy of chromosome 7 (mUPD7), which is usually identified in about 5–10% of cases (Kotzot et al., 1995; Netchine et al., 2007), and methylation abnormalities of the 11p15.5 region in about 40–50% of cases (Gicquel et al., 2005; Netchine et al., 2007). The cause currently remains unknown in many patients. On the other hand, a broad spectrum of phenotypes has been described: these vary from one individual to another according to etiology and severity. SRS is characterized by severe intrauterine and postnatal growth retardation, with relative macrocephaly at birth, typical dysmorphic features, and feeding difficulties (Wakeling et al., 2017). There may be additional clinical features, such as fifth finger clinodactyly, micrognathia, hypoglycemia, café-au-lait spots, genital anomalies, and premature adrenarche. SRS is currently diagnosed according to the clinical criteria of the Netchine-Harbison clinical scoring system (NH-CSS; Azzi et al., 2015). Recently, the NH-CSS was adopted as clinical definition of this syndrome by the first

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international consensus meeting on the diagnosis and management of SRS (Wakeling et al., 2017). Indeed, compared to other clinical scoring systems (Dias et al., 2013; Netchine et al., 2007), the NH-CSS is more sensitive (98%), it had the highest negative predictive value (89%) (Azzi et al., 2015; Wakeling et al., 2017) and the six criteria are clearly defined.

Thus far, research has focused mainly on the genetic and medical aspects of the syndrome, and rarely on patients' cognitive profile. Traditionally, intellectual functioning and cognitive profile are often considered to be normal (Bartholdi et al., 2008; Patton, 1988). However, the parents of children with SRS often express considerable concern about their cognitive development with regard to education, schooling, and autonomy. Indeed, cognitive weaknesses or impairments have a negative impact on the daily, academic/occupational, social lives, and, more generally, the quality of life in other genetic syndromes or neurodevelopmental disorders (Fuermaier, Fricke, de Vries, Tucha, & Tucha, 2019; Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015; Holst & Thorell, 2019; Udwin, Howlin, Daviesn, & Mannion, 2002). Better knowledge of the strengths and weaknesses of the cognitive profile of other disorders has helped optimize appropriate care and intervention across lifespan (Conners, Rosenquist, Arnett, Moore, & Hume, 2008; Mervis & John, 2010).

Several studies have documented the development of children with SRS, relying mainly on data yielded by clinical interviews with the children and their parents or else on their medical records. These studies found that some patients presented a cognitive developmental delay, encompassing mild motor delay, learning difficulties, and delayed speech (Azzi et al., 2015; Bruce, Hannula-Jouppi, Peltonen, Kere, & Lipsanen-Nyman, 2009; Fuke et al., 2013; Netchine et al., 2007; Smeets, Renes, van der Steen, & Hokken-Koelega, 2017; Wakeling et al., 2010). Some behavioral problems (e.g., attention-deficit problems or attention-deficit hyperactivity disorder, autism spectrum disorder) were also reported, but were uncommon (Azzi et al., 2015; Wakeling et al., 2010). Although these studies inform us about the difficulties encountered in this syndrome, we have no information concerning their severity or how they were assessed or diagnosed.

To our knowledge, only five studies and three case reports have specifically documented the intellectual and cognitive profile of children and adults with SRS. However, in most of these studies, patients were diagnosed according to nonstandardized clinical criteria and not confirmed on molecular basis (Lai, Skuse, Stanhope, & Hindmarsh, 1994; Noeker & Wollmann, 2004; Plotts & Livermore, 2007; Schlegel, Arcona, Morgan, & Hatt, 2000; Sieńko et al., 2010). Indeed, their patients were diagnosed using various clinical criteria, some of which are currently not in the definition of the SRS (e.g., the presence of clinodactyly). In Karher and Banda (2017), the diagnostic criteria were not specified. Therefore, we cannot be certain that all the patients in these studies did have SRS. Thus, the results should be interpreted with caution. Only studies by Patti, Coutinho, Doummar, and Netchine (2016) and Patti et al. (2018) have presented patients with SRS confirmed by molecular diagnosis. Although we should be cautions in interpreting these studies, they do provide some evidence for certain strengths and weaknesses in the intellectual profile of people with SRS.

First, these studies indicate that for most people with SRS their intelligence falls within a normal range, but it is slightly below average. Lai et al. (1994) were the first to investigate cognitive functioning in children with SRS. They assessed intellectual functioning and reading abilities. Results were compared with normative data and showed that, on average, the children's Full-Scale Intelligence Quotient (FSIQ) was significantly lower ($M = 85.9$, $SD = 23.7$, $p < 0.01$) than that of the general population ($M = 100$, $SD = 15$). The results of Noeker and Wollmann (2004) supported the findings of Lai et al. (1994), but the observed differences were significantly smaller than previously observed. The children with SRS had an FSIQ score still significantly lower (−4.3 points, $p < 0.05$) than that of the age-matched reference norms and their sibling (−8.08 points, $p < 0.05$). A recent study in Poland also found similar results (Sieńko et al., 2010). Children's results showed that their mean IQ was significantly lower (11.8 points, $p < 0.001$) than that of the general population (normative data), but with a similar range of values. A recent study by Patti et al. (2016) involved the cognitive assessment of 30 children with SRS (some with 11p15 epimutation, some with mUPD7). Results showed that their mean IQ was 6.6 points lower (range = 52–118) than that of the general population. The mean FSIQ of the 11p15 epimutation group was 3.9 points higher than that of the mUPD7 group. There are few studies showing the intellectual development of individuals with SRS in adulthood. The reported cases showed that the intellectual functioning was heterogeneous: a young man had upper average intelligence (Plotts & Livermore, 2007), a young woman had a delayed mental development (Karher & Banda, 2017), another

man displayed a mild cognitive delay and six had normal intelligence (Patti et al., 2018). These case studies provide some insight into the intellectual profile of adults with SRS, but this profile needs to be confirmed by studies with larger samples of adults with SRS.

On the whole, the majority of individuals with SRS had normal intelligence, but a heterogeneous intellectual profile in favor of verbal skills. Indeed, verbal abilities were higher than nonverbal abilities in many studies (Lai et al., 1994; Patti et al., 2016; Plotts & Livermore, 2007). However, several difficulties have also been observed in patients with SRS. It would seem to be more at risk of developing learning and even cognitive disabilities. In a study by Lai et al. (1994), several children had impaired arithmetic and reading abilities. A most of children had needed speech therapy (Lai et al., 1994), especially those with mUPD7 in the Patti et al. (2016) study. When Schlegel et al. (2000) explored the neuropsychological functioning of an 8-year-old boy with SRS, they found that he presented a diffuse pattern of deficits, including language and motor deficits. The young man described by Plotts and Livermore (2007) presented a mild nonverbal learning disabilities syndrome (NLDs). NLDs is characterized by basic neuropsychological deficits in visuospatial processing, psychomotor coordination, social-emotional functioning, and impairments in academic abilities (especially mathematics), while some individuals also display attention deficits (Fine, Semrud-Clikeman, Bledsoe, & Musielak, 2013). Furthermore, some patients presented attention or concentration difficulties (Karher & Banda, 2017; Plotts & Livermore, 2007).

If these studies in children and adults provide knowledge about intellectual profile, they must be confirmed with a largest sample and patients with SRS diagnosed according to clinical diagnosis confirmed by molecular diagnosis. Furthermore, in some genetic syndromes such as Down syndrome (Grieco et al., 2015) or 22q11.2 deletion syndrome (Swillen & McDonald-McGinn, 2015), neurocognitive and neurobehavioral profiles emerge within specific developmental periods. It is therefore important to evaluate the intellectual functioning and cognitive abilities of individuals with SRS across lifespan, not just in childhood. To our knowledge, no published studies have yet assessed the intellectual profile in adults. This was the main aim of this exploratory study. In order to do this, we collected information on intelligence and strengths/weaknesses of the intellectual profile of adults with SRS. Guided by the literature in children and adults, it was hypothesized here that individuals with SRS would have normal intelligence, but with a specific intellectual profile. We predict that verbal abilities will be better than nonverbal abilities and adults will experience difficulty in processing speed in light of reported attention difficulties. Thus, we analyzed the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) scores of 10 adults with SRS to determine whether a specific profile emerged in comparison with normative scores on the WAIS-IV.

Materials and methods

Participants

Ten adults with SRS (six men and four women), aged 18–39 years ($M = 23.7$, $SD = 6.6$ years) were included in this study between July 2016 and February 2018. All participants had SRS due to epimutation in the 11p15 region. Participants were recruited all over France from one of four sources: The Referral Center at Trousseau Children's Hospital in Paris, the genetics departments of university hospitals in France, and two French patient associations ("Association Française des Familles touchées par le Syndrome de Silver-Russell et des personnes nées Petites pour l'Age Gestationnel" et leur amis and "Association Grandir"). Letters were sent to patients inviting them to participate on a voluntary basis. Inclusion criteria were (a) clinical diagnosis of SRS (Wakeling et al., 2017) confirmed by a molecular diagnosis, (b) over 18 years old, and (c) French speaking. According to the NH-CSS, the clinical diagnosis is made when patients meet at least four of the following six clinical criteria: born small for gestational age (birth weight and/or birth length, ≤ -2 *SD*s below mean weight for gestational age); postnatal growth retardation (height at 24 months ≤ -2 *SD*s below mid-parental target height); relative macrocephaly at birth; prominent forehead at the ages 1–3 years; body asymmetry; feeding difficulties and/or low body mass index (BMI; ≤ -2 *SD*s below mean BMI at 24 months) during early childhood (Azzi et al., 2015; Wakeling et al., 2017). Patients with SRS syndrome without diagnosis confirmed on molecular basis have been excluded, because although the NH-CSS assist the diagnosis, the accuracy of clinical diagnosis could be influenced by the experience of the clinical investigator (Eggermann, Begemann, Binder, & Spengler, 2010).

Informed consent was obtained from all patients before the intellectual assessment. The study was approved by the ethics committee of Rennes University Hospital, France (No. 15.123, 29/12/15),

and the data were collected in accordance with the Declaration of Helsinki.

Clinical and medical data

For each participant, the intellectual assessment was conducted in the individual's family home and therefore in their daily environment. Before the intellectual assessment, we conducted a semi-structured interview to collect:

- *Demographic characteristics*: patient sex, age, academic achievement, and educational pathway.
- *Medical data*: Patients were asked questions concerning: (a) NH-CSS criteria; (b) past treatments (GH and gonadotropin-releasing hormone analog (GnRHa) therapy); clinical and medical features such as the presence or absence of genital anomalies, a fifth finger clinodactyly, café-au-lait spots, orthodontic problems, scoliosis, diabetes, episodes of hypoglycemia, a delayed speech, and a motor delay during childhood; and (c) current and past rehabilitation (e.g., language therapy). Medical data were also taken from patients' medical records with the consent of the patient.
- *Daily difficulties and parental concerns*: Patients were asked questions concerning daily difficulties during the semi-structured interview (e.g., fatigability). Two questionnaires were also completed one to two months later, they were returned by mail: one by patients and one by their parents. The questionnaire for patients included one question: "Do you currently have any difficulties or concerns about your functioning in any of these areas of your daily life: (a) attention/concentration, (b) memory, (c) learning difficulties, (d) social development, (e) language, (f) motor function, (g) self-esteem, (h) autonomy. Only the areas in which difficulties were noted by patients were reported in this study. The questionnaire for their parents included one open question: what are your concerns for your child?

The intellectual assessment and interview were conducted by a psychologist. The presence of patients' parents was not a mandatory criterion, but when their parents were present in the family home, the psychologist took time to have a conversation with them. This allowed us to complete some information that was not given by patients. The entire assessment, including the interview, lasted three hours on average.

Intellectual functioning

We administered the French-language version of the WAIS-IV (Wechsler, 2011) to assess patients' intellectual profile. The WAIS-IV is widely used to examine cognitive profile in genetic (e.g., Lehman et al., 2017), neurodevelopmental (e.g., Bucaille et al., 2016), or psychiatric conditions (e.g., Michel et al., 2013), because it has good psychometric properties (validity and reliability). This scale contains 10 main subtests and five supplemental subtests (Comprehension, Figure Weights, Letter-Number Sequencing, Picture Completion and Cancellation). The main subtests allow the FSIQ to be calculated, together with four domains of cognitive functioning: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). VCI, which evaluates language skills, is based on three subtests: Similarities, Vocabulary and Information. PRI assesses fluid reasoning in the perceptual domain and again is based on three subtests: Block Design, Matrix Reasoning and Visual Puzzles. WMI measures short-term memory and attention via the Digit Span and Arithmetic subtests. PSI evaluates the ability to process visual information quickly, with concentration and eye-hand coordination, via two subtests: Symbol Search and Code.

We compared the intellectual data of the adults with SRS with those of the French normative sample on the WAIS-IV. The constraints of this study did not allow us to use a control group recruited at the time of this study. However, the normative data of the WAIS-IV has been thoroughly validated in a French population and permitted us to make comparisons with a normative group. Indeed, data has been collected on the WAIS-IV from a large normative sample (876 individuals aged 16 to 79 years and 11 months) which is representative of the French-speaking population and is stratified by age, sex, ethnicity, education level (number of school years completed), and geographical regions (Wechsler, 2011). The normative population mean is 100 ($SD = 15$) for index scores. Furthermore, the same methodology has been used in literature on this syndrome (e.g., Lai et al., 1994; Noeker & Wollmann, 2004) and will allow for comparisons between our study and previous studies.

For each participant, we calculated mean index scores and discrepancies between these indices in accordance with the WAIS-IV test manual, by the appropriate age of the participant and based on the overall sample (Wechsler, 2011). We performed six comparisons of the index scores: VCI/PRI, VCI/WMI, VCI/PSI, PRI/WMI, PRI/PSI, and WMI/PSI. The

significance level for all comparisons was set at the 0.05 level.

In accordance with the test manual, scores were only classified as *clinically significant* if they were obtained by no more than 2,5% ($SD \leq 2$) of the normative population. Therefore, in our study, scores below 70 were classified as *clinically significant* (Wechsler, 2011).

Data analyses

We ran the statistical analyses on SPSS, version 20.0. The significance threshold was set at 0.05, but the trend results will be analyzed when p is between 0.10 and 0.05. We used the Shapiro-Wilk normality test to confirm that the distribution of our variables followed a normal distribution. It was systematically confirmed by an inspection of the Q-Q plot. Thus, we favored the use of parametric statistical tests. We carried out descriptive statistics, a one-sample t-test on the overall score and on each index to establish the intellectual profile of adults with SRS in comparison with the normative data. A Bonferroni correction was utilized for correction of the Type I errors. For the one-sample t-test, the Bonferroni correction was $p < 0.01$ for the overall FSIQ and the four index scores on the subscales. For the profile analysis, the potential difference between the four index scores within our group of Silver-Russell individuals was examined using a repeated-measures analysis of variance (ANOVA). Paired samples t-test with the Bonferroni correction were used to examine the discrepancies between the indices within patients in order to study strengths and weaknesses within our group. The effect sizes were summarized using Eta-squared (η^2) and Cohen dz statistic (Cohen, 1988; this amounts to a Cohen's d for within-subjects design). Finally, unpaired samples t-tests was used to investigate the association between sex, treatments (GH and GnRHa) and the FSIQ score, and a linear correlation (Pearson correlation) was conducted between education level and the FSIQ score.

Results

Clinical and medical data

Table 1 shows the clinical and medical features of adults with SRS in the current study. All the patients had at least five of the six clinical characteristics listed in the NH-CSS (Wakeling et al., 2017), and five patients had all six characteristics. However, some data were lacking such as data on protruding forehead, which must be assessed either in the first two years of life or else in adulthood, based on photographs of the individuals aged 1–3 years (Wakeling et al., 2017). Most adults had received growth hormone therapy (GH) during childhood and the mean duration of the GH treatment was 119.33 months ($SD = 60.87$). Four men had genital anomalies (hypospadias, cryptorchidism) and one woman had genital malformations (SRS associated with Mayer-Rokitansky-Kuster-Hauser syndrome). Two patients had Type 2 diabetes, while three other adults also presented a risk of prediabetes, with insulin resistance or carbohydrate intolerance. Episodes of hypoglycemia had been noted or documented in three patients during childhood. Delayed motor development was frequently reported during childhood. The mean age at which patients reported taking their first steps was 19 months ($SD = 4.40$).

Table 1. Clinical and medical characteristics in adults with SRS.

Gender	
Male	6/10
Female	4/10
Mean age in years (SD)	23.7 (6.6)
NH-CSS clinical diagnosis	
Small for gestational age	10/10
Postnatal growth failure	8/9[a]
Relative macrocephaly at birth	7/7[a]
Protruding forehead	9/9[a]
Body asymmetry	10/10
Feeding difficulties	10/10
Past treatment	
Growth hormone treatment	6/10
Gonadotropin-releasing hormone analog	5/10
Clinical and medical features	
Genital anomalies	5/10
Café-au-lait spots	3/8[a]
Fifth finger clinodactyly	9/10
Orthodontic problems[b]	9/10
Scoliosis	5/10
Diabetes	2/10
Episodes of hypoglycemia	3/10
Delayed speech[c]	4/10
Motor delay[c]	7/10

Note. SRS = Silver-Russell syndrome.
[a]Missing data for some variables are due to the absence of these information in the medical record.
[b]Orthodontic problems including micrognathia and irregular teeth or crowded teeth.
[c]During childhood.

Education and rehabilitation

All patients had been in mainstream education (Table 2), but two had been assisted in the classroom for a time by a special education needs assistant to cope with learning difficulties. Nine adults had successfully completed high school and obtained the French high-school diploma (baccalaureate). Some patients (70%) had gone on to higher education. The

Table 2. Other characteristics and difficulties/concerns reported by participants and their families.

Education	%
Mainstream education	100
Average number of years of education (SD)	12.9 (1.85)
Current and past rehabilitation	
Speech therapy	70
Physiotherapy	50
Psychomotricity	30
Oculomotor therapy	30
Psychological therapy	60
Reported daily difficulties	
Learning difficulties	60
Attention/concentration	60
Memory	10
Language	30
Writing difficulties	30
Fatigability	40
Social development	30
Self-esteem	60
Parental concerns	
Working life	30
Emotional life	70

mean level of education was 12.9 years ($SD = 1.85$). Many patients received rehabilitation in childhood, and some were still receiving it at the time of the study. Many patients underwent language therapy (70%), physiotherapy (50%), psychomotricity therapy (30%), oculomotor therapy (30%), and neuropsychological/psychological therapy (60%).

Reported daily difficulties and parental concerns

Table 2 also shows the perceived difficulties and concerns reported by participants and their parents. The majority of patients believed they had learning difficulties (60%), especially attention/concentration difficulties (60%). Learning disabilities were identified in two adults when they were children (diagnosis of dyslexia for one and diagnoses of dyslexia and attention deficit for the other). Perceived difficulties in memory (10%), language (30%), or writing (30%) were less often reported by adults. Some stated that they always feel tired or have the impression of being tired more easily than other people of the same age (40%). Most adults reported experiencing negative feelings associated with low self-esteem (60%). Parental concerns mainly about their children's emotional lives (70%). In this study, most adults with SRS were single and childless.

Intellectual functioning

Description and comparison with the normative data

The Shapiro-Wilk normality test indicated that the FSIQ, VCI, PRI, WMI, and PSI scores were all normally distributed ($p > 0.05$). It was systematically confirmed by an inspection of the Q-Q plot.

Table 3. Differences in mean index scores between adults with SRS and normative data.

Index	Mean (*SD*)	Range	*p* value*
FSIQ	95.4 (18.55)	71–127	0.453
VCI	109.1 (19.09)	79–133	0.166
PRI	90.6 (16.39)	74–128	0.103
WMI	90.7 (19.55)	63–117	0.167
PSI	91.1 (15.01)	69–111	0.094

Note. SRS = Silver-Russell syndrome; FSIQ = Full Scale Intelligence Quotient; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index.
*$p < 0.01$.

The mean FSIQ score was 95.40 ($SD = 18.55$, range = 71–127) (see Table 3). Statistical analysis with one-sample *t*-test showed that the mean FSIQ score did not differ statistically from the test reference value of 100 ($t(9) = 0.784$, $p = 0.453$). FSIQ was in the average range for 50% of adults with SRS (FSIQ between 90 and 109). In our sample, no individual had an FSIQ score < 70 and therefore no one reached the threshold for clinical significance. However, three adults had a score in the borderline range (FSIQ between 70 and 79). One adult had an above average FSIQ score (FSIQ between 110 and 119), and one adult had an FSIQ score in the superior range (FSIQ between 120 and 129).

Mean VCI, PRI, WMI and PSI scores did not differ from those of French normative sample on the WAIS-IV. Thus, the patients in our study did not have averages below or above the normative data for verbal comprehension, perceptive reasoning, working memory, or processing speed.

Analysis of strengths and weaknesses within SRS group

The repeated-measures ANOVA examining potential differences between the four index scores was significant ($F(3,27) = 6.536$, $p = 0.002$, $\eta^2 = 0.421$). Performance on each of the indices was compared using a paired samples *t*-test. These analyses indicated that the mean VCI was significantly higher than either the mean PRI ($t(9) = 3.647$, $p < 0.032$, $dz = 1.15$), mean WMI ($t(9) = 3.694$, $p < 0.030$, $dz = 1.17$), or mean PSI ($t(9) = 3.748$, $p < 0.027$, $dz = 1.19$) scores (Table 4). These results show that the verbal comprehension is one of the strengths in the cognitive profile of patients with SRS.

Furthermore, this analysis revealed significant discrepancies in individual performances. The majority of patients had VCI scores that were significantly higher than their PRI (50%), WMI (70%), and PSI

Table 4. Comparisons between index scores in adults with SRS.

	Score 1		Score 2			
Index comparison	Mean	SD	Mean	SD	Diff. of means (*SD*)	*p* value
VCI_1 vs. PRI_2	109.10	19.09	90.60	16.39	18.50 (16.04)	0.032*
VCI_1 vs. WMI_2	109.10	19.09	90.60	16.39	18.40 (15.75)	0.030*
VCI_1 vs. PSI_2	109.10	19.09	90.60	16.39	18.00 (15.19)	0.027*
PRI_1 vs. WMI_2	90.60	16.39	90.70	19.55	−0.10 (18.18)	0.986
PRI_1 vs. PSI_2	90.60	16.39	91.10	15.01	−0.50 (11.39)	0.893
WMI_1 vs. PSI_2	90.70	19.55	91.10	15.01	−0.40 (18.50)	0.947

Note. SRS = Silver-Russell syndrome; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index. The left's index corresponds to score 1 and the right's index corresponds to score 2.
*$p < 0.05$.

Table 5. Significant discrepancies between the index scores in adults with SRS.

	Significant discrepancy (%)	Clinically significant (%)[a]
VCI > PRI	50	20
VCI < PRI	0	0
VCI > WMI	70	20
VCI < WMI	0	0
VCI > PSI	50	10
VCI < PSI	0	0
PRI > WMI	30	0
PRI < WMI	20	10
PRI > PSI	10	0
PRI < PSI	10	0
WMI > PSI	20	0
WMI < PSI	10	0

Note. SRS = Silver-Russell syndrome; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index.
[a]Clinical significance set at level discrepancy <2,5% of the normative base rate.

(50%) scores. Other discrepancies are reported in Table 5.

Associations/correlations

The FSIQ score did not differ statistically according to sex ($t(8) = 0.880$, $p = 0.405$), GnRHa treatment ($t(8) = 0.875$, $p = 0.407$) and GH therapy ($t(8) = 0.689$, $p = 0.510$). A correlation between the FSIQ score and education level suggested that the two were positively associated. However, this correlation is not significant ($r = 0.586$, $p = 0.075$).

Discussion

The present study was designed to identify the intellectual profile of French adults with SRS. Results showed that our adults with SRS had a mean FSIQ score in the average range. They had better verbal IQ scores than their scores on the other indices. They reported frequent daily difficulties such as learning difficulties and low self-esteem.

Clinical and medical characteristics

The SRS diagnosis had been made in late childhood for some patients, but all clinical diagnoses were confirmed by a molecular diagnosis. Our group consisted exclusively of adults with 11p15 epimutation. All patients had at least five of the six clinical characteristics of the NH-CSS, and several patients had all six, consistent with the literature on patients with 11p15 epimutation (Wakeling et al., 2017). Our results were similar to those reported by Azzi et al. (2015). However, some early growth data were lacking. Most of the adults had received GH therapy and GnRHa treatment during childhood, as GH therapy is recommended for this syndrome. This therapy can improve growth, body development and muscle mass (Smeets, Zandwijken, Renes, & Hokken-Koelega, 2016), and also has potential benefits in terms of psychomotor development and appetite (Wakeling et al., 2017). Premature adrenarche and central precocious puberty are reportedly as frequent in SRS. In some cases, treatment with GnRHa may be used in association with GH treatment to preserve adult height potential (Wakeling et al., 2017). Motor delay was more frequently reported in our group. Mean age at first steps was 19 months ($SD = 4.40$). Patients reported that they had experienced greater difficulties with gross and fine motor skills as children than their peers did. Their motor delay may have been related to reduced muscle bulk associated with a fairly large head size (Wakeling et al., 2010; 2017). Some patients had a metabolic complication, more specifically Type 2 diabetes. Several studies have reported cases of adults with SRS who develop a range of other metabolic complications besides diabetes, including testosterone deficiency and hypercholesterolemia (Searle & Johnson, 2016; Takenouchi, Awazu, Eggermann, & Kosaki, 2015). Individuals born with a low birth weight, including children with SRS, are at increased risk of developing metabolic complications in adulthood (Barker, 2004; Wakeling et al., 2017). Patients with SRS, therefore, need to receive medical follow-up in adulthood to prevent or manage metabolic problems.

Reported daily difficulties and parental concerns

Most adults also reported having low self-esteem, and parental concerns essentially focused on their children's emotional lives. A recent study in the United Kingdom that investigated the psychosocial impact of SRS (Ballard et al., 2019) found similar results. The adults in this study with SRS reported appearance-related concerns (not only related to height), which can result in psychological distress (e.g., anxiety, depression, low self-esteem) and difficulties in relationships. The prevention and management of psychosocial problems should, therefore, be a priority across childhood, adolescence, and adulthood, in order reduce the risk of psychological distress and social withdrawal. All patients had been in mainstream education, but two had received special assistance along the way for learning difficulties. Nine adults had earned their high-school diploma and seven had gone on to higher education. Many patients had received early interventions and multidisciplinary care in childhood. Some had undergone language therapy, physiotherapy, and psychomotricity therapy for speech and motor delays. Neuropsychological/psychological therapy had been provided for learning difficulties and/or psychosocial difficulties. Most of the patients and their families reported learning difficulties, especially attention/concentration difficulties. Similar difficulties have already been described in some pediatric cohorts (Azzi et al., 2015; Bruce et al., 2009; Fuke et al., 2013; Lai et al., 1994; Wakeling et al., 2010). Some memory difficulties, language problems and writing difficulties were reported, but with a lower frequency.

Intellectual functioning

Overall, our results were in line with our hypotheses. Ten adults with SRS in our study achieved a mean FSIQ score of 95.40 ($SD = 18.55$), which is 4.6 points below the mean for the normative data, but this difference was not significant. This result is similar to those of previous studies in pediatric cohorts. Lai et al. (1994) found a score that was lower by 14.1 points and Sieńko et al. (2010) a score that was lower by 11.8 points, while Noeker and Wollmann (2004) and Patti et al. (2016) reported smaller differences of 4.28 and 6.6 points. Thus, the mean FSIQ score being in the average range confirms that our adults with SRS have a normal intellectual capacity. Although, we expected difficulties in processing speed in light of reported attention difficulties, in our study, no significant difference was found for the processing speed score. This was an unanticipated result considering that most of the patients in our groups reported learning difficulties, especially problems with attention/concentration difficulties. The processing speed score measures the ability to process visual information quickly, with concentration and eye-hand coordination (Wechsler, 2011), but it also probes short-term memory and attention (specifically visual attention). Thus, we expected this index to be influenced by attention disorders in a few patients. It would be interesting to study these attention difficulties in a larger sample and by administering a standardized assessment, such as the d2-R test (Brickenkamp, Schmidt-Atzert, & Liepmann, 2015), to have a better picture of specific attention challenges for adults with SRS. We also observed discrepancies between the index scores of the WAIS-IV tests in our patients with SRS, who had a high mean verbal comprehension score. This result echoes those of Patti et al. (2016)'s and Plotts and Livermore (2007)'s studies. Patti et al. (2016) further observed that the mean verbal comprehension score was only higher than the other mean index scores in the group with 11p15 epimutation. No such difference was found in the group with mUPD7. We can therefore surmise that this is a specific feature of the intellectual profile of individuals with 11p15 epimutation. Therefore, verbal comprehension is a real strength within intellectual profile of patients with SRS in our group. This strength can be a lever on which to rely to support patients with SRS in learning, but also during interventions such as rehabilitation or remediation.

In our study, neither sex nor GH or GnRHa past treatment were associated with the FSIQ score. However, recent studies suggest possible beneficial effects of GH on cognitive development in patients with GH deficiency and Prader-Willi syndrome (Höybye, Thoren, & Böhm, 2005; Nyberg & Hallberg, 2013; Siemensma et al., 2012). Other studies suggest that it specifically improves attention and memory (Falleti, Maruff, Burman, & Harris, 2006). The effects of GnRHa treatment are more contrasted in the literature. Negative effects were reported especially on verbal episodic memory and working memory (Craig et al., 2007). Other studies concluded that there was no associated cognitive impairment (Wojniusz et al., 2016). A recent study in small for gestational age children showed that combined GH/GnRHa treatment has no long-term negative effects on cognition, compared with GH treatment only (Goedegebuure, van der Steen, de With, & Hokken-Koelega, 2018). The effects of GH and GnRHa require further studies and particular on long-term effects. In addition, some of

our patients had Type 2 diabetes. This metabolic disorder can reduce memory, processing speed, and executive function gradually over time (Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014). These cognitive dysfunctions seem to start slowly in the prediabetic stages (Koekkoek, Kappelle, van den Berg, Rutten, & Biessels, 2015). Type 2 diabetes could change the cognitive profile of patients with SRS on the long-term.

In all previous studies apart from Patti et al. (2016), patients were diagnosed solely on clinical criteria and not confirmed on molecular basis. As inclusion was based only non-standardized clinical criteria, false positives may have been included in these groups, thus distorting the results. This would explain the IQ differences across studies and clinical criteria. One of the strengths of the present study is that the patients' diagnosis was based on the NH-CSS (Azzi et al., 2015; Wakeling et al., 2017) and confirmed by molecular diagnosis. Furthermore, our patients formed a homogeneous sample, as their SRS was systematically due to epimutation in the 11p15 region. Therefore, this study provides evidence for a specific intellectual profile for patients with 11p15 epimutation.

Our results are consistent with data on 11p15 epimutation in the literature. Several studies have shown phenotypic variability according to the etiological causes of SRS (Azzi et al., 2015; Bruce et al., 2009; Fuke et al., 2013; Wakeling et al., 2010, 2017). Clinical characteristics (e.g., asymmetry and congenital anomalies) are more commonly seen in the 11p15 epimutation, but cognitive or behavioral problems seem less common. By contrast, mUPD7 patients have been shown to present more speech delays, learning difficulties, and behavioral problems. For example, in the study of Noeker and Wollmann (2004), the two patients with a diagnosis of mUPD7 also had markedly lower IQ scores (81 and 84), and in the study by Patti et al. (2016), the mUPD7 group had a lower IQ (−3.9 points) than the 11p15 group. Molecular etiology could be a risk factor for neurocognitive development.

Another strength of this study is that it is the first to have documented the intellectual functioning of adults with SRS using a standardized intelligence assessment (WAIS-IV) that affords greater sensitivity in the measurement of intellectual functioning and cognitive domains (working memory, processing speed, etc.). Thus far, the majority of studies have focused only on pediatric cohorts, and not on adolescence and adulthood. Our study therefore brings new knowledge about adulthood. It would, however, be interesting to conduct a longitudinal study of the cognitive outcomes of children with SRS into adulthood.

Limitations and future directions

The present study nonetheless had several limitations. First, our sample consisted of a small group of adults with SRS who have volunteered to take part, possibly introducing a bias. It would thus be interesting to increase the number of patients, in order to confirm and generalize these results. The present study did not have a control group. Future research should investigate these questions with a control group which presents the same characteristics as adults with SRS group (e.g., age, gender, and education level).

Second, one of the strengths but also limitation of our study is that our group only contained patients with SRS due to epimutation of the 11p15 region. Future studies should, therefore, include patients with other genetic alterations (mUPD7), in order to explain the cognitive profile(s) of individuals with SRS better. Third, we only investigated intellectual functioning. A more comprehensive neuropsychological assessment (attention, executive functions, reading and writing skills, etc.) would help to bring the cognitive profile of adults with SRS into sharper focus.

Finally, although our study improves and expands knowledge about SRS, more research is needed to explore patients' cognitive profiles. Better knowledge would allow individuals with this syndrome to receive targeted interventions, education and/or therapy adapted to their cognitive profile. Cognitive remediation program, for example, appears especially suited to target attention difficulties that were reported by our patients (Stevenson, Whitmont, Bornholt, Livesey, & Stevenson, 2002).

In conclusion, this is the first study to have documented the intellectual functioning of adults with SRS. We found that adults with 11p15 epimutation generally had normal intellectual efficiency, with better verbal IQ compared with the other indices. The consistency of reports on intellectual functioning in both child and this study's adults with SRS lends increased support to the hypothesis of specific intellectual profile in this syndrome. Although both the adults and their families reported frequent daily difficulties, most of the patients had been able to graduate from high school and go on to higher education. Early intervention and multidisciplinary care from childhood to adulthood is important in SRS for care

potential medical, cognitive, and psychosocial problems.

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Disclosure statement

The authors declare that there are no conflicts of interest in this study.

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