P1-P817

Silver-Russell Syndrome with 11p15 epimutation: clinical analysis of adrenarche, central puberty and body mass index in a cohort of French children

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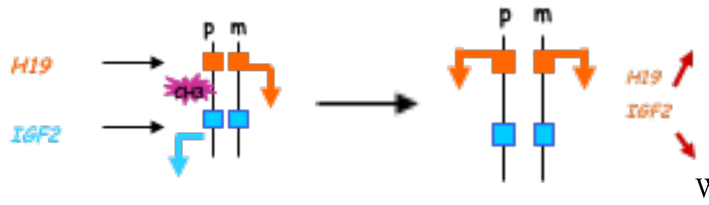
BACKGROUND

Silver-Russell Syndrome (SRS) is a clinically heterogeneous syndrome, related to 11p15 ICR1 loss of methylation in up to 50% of the cases. The clinical diagnosis has been recently revised in the first SRS international consensus. According to the Netchine-Harbison Clinical Scoring System (NH-CSS), it is considered if a patient has at least 4 of 6 of the following criteria: small for gestational age, postnatal growth failure, relative macrocephaly, protruding forehead, body asimmetry and feeding difficulties. Some patients may exhibit signs of early central puberty or signs of premature adrenarche, including an exaggerated adrenarche. Despite characteristic feeding difficulties, some children develop a rapid weight catch-up, probably when overfed, resulting in a marked body mass index (BMI) gain.



Gicquel *et al*. Nat Gen, 2005
Netchine *et al*. JCEM, 2007
Wakeling EL *et al*. Nat Rev Endocrinol, 2016

The normal 11p15 ICR1 region **Loss of methylation at 11p15 ICR1in SRS patients**

OBJECTIVES

To analyse the clinical features of a group of 11p15 SRS children, regarding signs of adrenarche, signs of central puberty, anthropometric data and metabolic data.

METHODS

We analysed retrospectively 40 SRS patients, ranging from 2,5 to 28 years old. All patients were clinically diagnosed scoring 4 to 6 clinical criteria of the NH-CSS. Besides that all patients were molecularly diagnosed with 11p15 epimutation. The children have been followed at the Paediatric Endocrinology unit of the Armand Trousseau Hospital outpatient clinic, in Paris, France. The following data were collected: anthropometric data, including height (H), weight and body mass index (BMI) from birth and from prepubertal period to pubertal period until final height (FH), when available; age of adrenarche onset (clinical and/or biochemical); age of thelarche in girls or testicular enlargement in boys (central puberty (CP) onset); prepubertal dehydroepiandrosterone sulfate (DHEAS) levels and baseline insulin-like growth factor 1 (IGF-1) levels (prepubertal period without growth hormone (GH) treatment).

A BMI SDS increase of at least 1.0 SD, 12-24 months before adrenarche and/or CP onset, was considered as a marked BMI gain. When the DHEAS levels were above the prepubertal reference range and the clinical signs of adrenarche (mainly pubarche) started before 8 years in girls and 9 years in boys, the child was considered to have premature adrenarche. Exaggerated adrenarche was defined as high DHEAS level for chronological age, even above pubertal range. Central precocious puberty (CPP) was clinically defined when the development of secondary sexual characteristics started before 8 years in girls and before 9 years in boys.

Table 1: Anthropometric data
Total population study n=40

Boys : Girls	20 : 20
Mean birth weight SDS	-3.0 (-4.7 to -1.3)
Mean birth length SDS	-4.4 (-8.6 to -0.9)
Mean head circumference SDS	-0.9 (-3.2 to 3.4)
Mean H SDS at 24 months	-3.2 (-7.5 to -0.1)
Mean BMI SDS at 24 months	-2.2 (-4.1 to 2.3)
Mean TH SDS	0.2 (-1.9 to 0.8)
Mean H SDS at puberty onset (with GH; n=20)	-1.2 (-4.3 to 0.9)
Mean H SDS at puberty onset (without GH; n=3)	-0.3 (-1.0 to 0.1)
Mean FH SDS (with GH; n=6)	-2.7 (-6.0 to -1.0)
Mean FH SDS – TH SDS	-2.4 (-6.5 to 0.4)

Table 2: Pubertal and metabolic data

Patients with adrenarche already diagnosed n=30		
Premature adrenarche	37 % (11/30; 7 boys)	
Exaggerated adrenarche	17 % (5/30; 3 boys)	
Mean age of clinical signs of adrenarche	Girls 8.5y	Boys 8y
Mean age of biochemical adrenarche	Girls 7.3y	Boys 6.9y
Patients with central puberty (CP) already dignosed n=24		
CPP	12% (3/24; 3 girls)	
Mean age of CP onset	Girls 9.1y	Boys 10.2y
Baseline IGF1 levels		
IGF1 SDS 0.0 to 2.0	57%	
IGF1 SDS ≧ 2.0	27%	
Patients with BMI evolution from prepubertal period to pubertal period n=31		
Marked BMI gain	52% (16/31; 9 boys)	

RESULTS

From the total of 30 patients with adrenarche already diagnosed, **37%** developed premature adrenarche, while exaggerated adrenarche was reported in **17%**, pointing out that adrenarche can be early and agressive in this population.Three girls **(12%)** presented with CPP. The appearance of clinical signs of adrenarche (8.5y for girls and 8y for boys) and of central puberty (9.1y for girls and 10.2y for boys) seems to be in the normal range, but in its lower limit.

Baseline IGF1 levels were between 0.0 and 2.0 SD in 57% of the cohort, and ≧ 2.0 SD in 27%. All patients with baseline IGF1 SDS ≧ 2.0 developed premature adrenarche and 40% of them also developed exaggerated adrenarche. The 3 girls with CPP had baseline IGF1 SDS ≧ 2.0 at prepubertal ages. BMI evolution from prepubertal period to pubertal period was available for 31 patients: 52% had a marked BMI gain. Premature adrenarche and/or exaggerated adrenarche were diagnosed in 67% and 14% of the patients with marked BMI gain, respectively. Final height was available for 6 patients, and 3 of them did not catch-up, regardless of GH treatment.

CONCLUSION

Premature and/or exaggerated adrenarche seem to be common among SRS 11p15 LOM patients, regardless of gender. The age of onset of adrenarche and central puberty processes seem to be earlier in these cohort than in the general population. A marked or a rapid increase in BMI may lead to premature adrenarche and early puberty. Further prospective studies are necessary to clarify these topics.

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