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A CASE WITH SILVER – RUSSELL SINDROME: THE EFFICACY OT TREATMENT WITH GROWTH HORMONE, Case report

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Abstract

Silver –Russell Syndrome (SRS) is rare syndrome, described in a separate way from Silver and Russel as a syndrome of "intrauterine dwarfism"with so many clinical phenotypes ranging from mild to classic (1,2). Different studies estimate the incidence of SRS that varies widely from 1:3000 to 1:100,000 people (2,3,4).

SRS is a heterogeneous disorder and the basic of the underlying defect is not known jet (3,5,6). Various molecular defects have been reported, mostly involving chromosomes 7 and 17 (7,8,9).

Here we present our first case in our Pediatric – Endocrinology Clinic,a 5 years old boy with a classic form of the syndrome. He had a severe deficit of height and weight (< -4DS) at presantation.GH deficiency, with no other hormonal deficits is established. He started treatment with growth hormone and had a good catch-up growth. After 11 years of treatment he achived a final height up to 159.7cm (-1.8DS), but although it was 0.5 SD less than his predicted height. The weight improvement was more slowly, not helping growth hormone therapy to have the best results.

Keywords: Silver –Russell syndrome, growth hormone.

Abbreviations: GH - Growth Hormone, SD – standard deviations

Introduction

Silver- Russell Syndrome (SRS), is both clinically and genetically a heterogeneous disorder and the basic underlying defect for this is not known (10). Except of other dismorphic features, this syndrome is also characterized by a slow growth before and after birth and is one of the reasons of the definitive short stature in males and females. Males with RSS can arrive a finale stature up to 151cm, and women with RSS up to 140cm (11,12,13).

There are over 400 case described in the literature with this syndrome, from the moment of its discovery, either classical or mild forms (14).

We are presenting our first case diagnosed with SRS in our clinic, followed for 11 years, and the results of his treatment with growth hormone (GH).

Case report

The child F.B., born 21.01 .1995, originates from the north of Albania was presented in our clinic at 21 .03. 2000, and was admitted in our hospital with the diagnosis: Short stature for exploration. In this moment he was 5 2/12 years old. His weight was 8 kg (<<- 4 DS aged matched), the height 92 cm (<< - 4 DS aged matched), bone age was -18mo-2yrs. His statural age at five yrs. was like a child of 30 months.

He was born in terme, from a normal pregnancy, but with a very low birth weight – 1300gr. Later on, he did not gain weight properly. He was very weak, lethargic in first days of life, did not eat well. He continued this way in the first 2 years of life mainly, with failure to thrive and in the same way even in coming years with a bad appetite, weak and without energy as a child.

He did not have infectious disease during infancy, besides some common viral infections.

In the physical examination at age of five years, you could see:

1. A very short child, but with a deeper deficit in weight,
2. A clear asymmetry of the body, with the right side shorter and thinner then the left side.
3. The head looks relatively bigger compared to the face and the whole body.
4. A small and triangle-looking face with expressed

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micrognatia and very irregular teeth especially in the low jaw.

5.Big ears in a relatively low position and a big nose

6.He has expressed clinodactilia of the 5 fingers (both hands)

7.His pubertal stage was A1P1G1 (1 /1.5 ml)

8.without learning disabilities

At his laboratory work, all biochemical examinations(urea, creatinine, liver tests, proteinogram, lipidograma, electrolytes)were normal range, except of fasting glicemia which was low (55 – 60mg/dl)and low level of iron (45 mcg/%) (Normal range:60-150mcg/%)

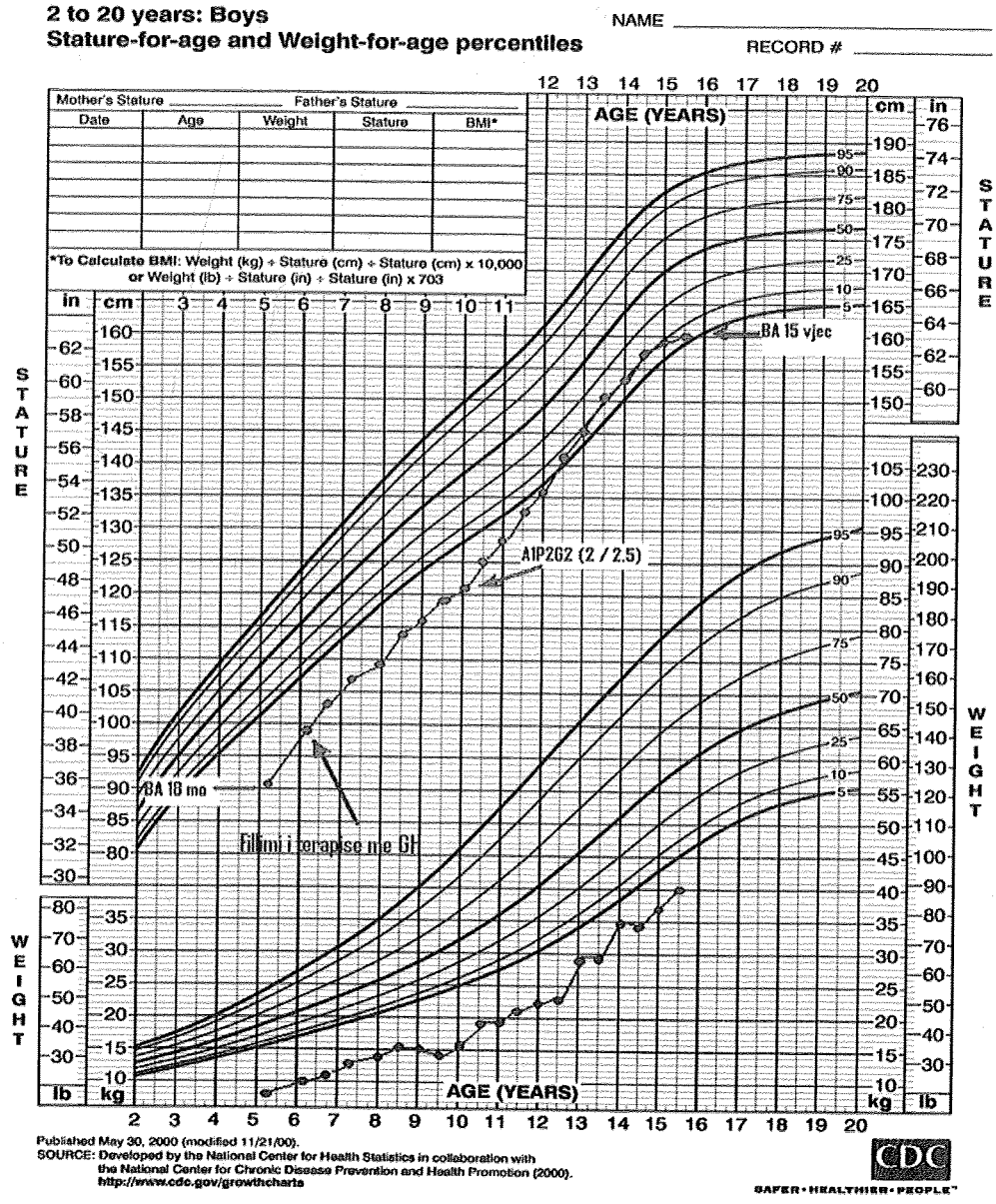
Coeliac Disease was excluded.
Ct –scan of head was normal.

Glucagon/propanolol stimulation test (for exploring growth hormone secretion) has very low level of groth hormone in the moments: -60, 0, +60, +90, +150, +180 min,respectively : 0.1,0.1,0.3,0.6.0.4,0.3 ng/ml.

IGF-1 - 60 ng/ml

Were not seen other hormonal deficits in the beginning.
TSH (ultrasensibel, IRMA AcM) 2.53 mUI/ L(N:0.17-4.04),FT4 – 16.5pg/ml (n:7-18), FT3-3.4pg/m l(n:2-4.25) Cortisolemia at 8AM -140ng/ml (n:55-230), Cortisolemia 8 PM -63.2ng/ml, (n:28-140), ACTH at 8AM-63.2 pg/ml (n:8-65), ACTH at PM-34.3pg/ml (n:7-30).
At the age 6 ½ yrs old, he started growth hormone therapy and recommended high calorie diet to the parents at home.
In this moment his weight was 10 kg<<< -4DS, height 99 cm< -4DS and the bone age was 3 yrs.

Graphic nr. 1. Growth chart of the child (F.B.) with SRS



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The GH's dose was 0.035- 0.04 mg/kg/bodyweight, 7 days a week. He tolerated it very well all the time, without any discomfort or complication.

During the first year of treatment, growth velocity (GV) from 7.6cm/year, went down to 6-6.5cm/year in continuing years and was high up to 8.5 – 9.8 cm /year during last 4 years of treatment, that corresponds with the time of his puberty.

During adolescence (at the year 2009) and under Growth hormone therapy – he developed a mild deficit of thyroid hormone (FT4 – 8.5 pg/ml, and TSH – 4.1mUI/L) for which he was treated with L-thyroxin,from 50mcg/a day in the beginning to 125 mcg/day at the end of our follow-up (28 .3 2011).

Growth hormone therapy was interrupted at the age 16 2/12 years, when bone age was also 15-16years, and GV –less then 2 cm in the last 6 months. He continues the treatment with L-thyroxin.

In the last control, at march 2011, at the age of 16 2/12 yrs. old weight was 40 kg (-2.7 SD) height was 159.7cm (- 1.8DC), Statural age was 14 ½ years old, the weight for his height has to be 51kg.

The predicted height of the child (Corrected midparental height) -CMPH-173.9cm

(max-180.4cm, min - 167.4cm)

Our child followed for 11 years, had very good results with growth hormone therapy arriving up to -1.8DS, although it was less then his predictive height (his corrected midparental height CMPH - was 173.9cm (max.180.4 and min 167.4cm).

His weight remained a little behind. In the final check he was -10 kg weight for his height (we are not sure for his diet regime at home).

Discussion

Silver Russell Syndrome (SRS) originally was described by Silver and colleagues in1953 and soon afterwards, by Russell in 1954.The first reports were in children with characteristic faces, low birth weight, asymmetry, and growth retardation (1,3,10,15). Children with this syndrome have slow growth before and after birth. Babies with this condition have a low birth weight and often fail to grow and gain weight at the expected rate, especially in their first years of life (failure to thrive) (3,11). The weight deficit is even bigger then height deficit even in continuity and from our experience, more difficult to be restored.

Over the past several years, more than 400 patients have been described with this syndrome, with phenotypes ranging from mild to classic (14,16).

Different studies estimates the incidence of SRS that varies widely from 1:3000 to 1:100,000 people (3,17).

SRS is both clinically and genetically a heterogeneous disorder and the basic of the underlying defect is not known (6,15,18). This syndrome usually occurs sporadically and its etiology is not identified in most cases. Various molecular defects have been reported, mostly involving chromosomes 7 and 17.

A few cases have been described with autosomal dominant transmission, including ring 2 chromosomes, balanced translocation of band17q25, and duplication of band 7p11.2-p13.

Nearly 10% of patients have proven Uniparental disomy (UPD) and abnormal methilation. Imprinting may play a role in the clinical phenotype of these patients (19,20).

Some other findings, also suggest that imprinting defects on chromosome 11 within the 11p15 region, may play a role in Silver-Russell Syndrome (19).

Those imprinted genes with a parent-of-origin specific expression are involved in various aspects of growth that starts from the prenatal period.

Over the past 20 years, it has become increasingly clear, that many of the so far known congenital imprinting disorders (IDs) are clinically characterized by growth disturbances. This is well established for Angelman, Prader Willi, and Beckwith -Wiedemann syndromes. Finding imprinting defects in patient with Silver-Rusell Syndrome (SRS) is a relatively new discovery (21).

Patho-physiology & clinical presentation

Growth failure is the primary abnormality. Patients typically present with intrauterine growth retardation, feeding difficulty, failure to thrive, or postnatal growth retardation. Adequate catch up growth often does not occur, and the final height still is less then normal (< - 3.6 standard deviation) (11,13).

Other symptoms that the disease can present is body asymmetry, clinodactilia of the fifth finger, delayed bone age, gastro-esophageal reflux, kidney problems like: horseshoe kidney, hydronephrosis, posterior urethral valve, renal tubular acidosis, large

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heads for body size, poor growth, short stature, short arms, wide forehead with a small triangle-shaped face and small narrow chin (3).

There are no specific laboratory tests to put the diagnosis of Silver Russell Syndrome. The diagnosis is based on the judgement of the clinicist, the pediatrician.

Diagnostic criteria are not strictly established. The group of doctors that have been studying patient with SRS (1,15,16,22) proposed that the positive diagnosis can be when the child has at least 4 of the following features:

- Birth weight less than or equal to -2DS from the mean.
- Postnatal growth, less or equal to -2DS, from the mean at diagnosis.
- Preservation of occipito-frontal circumference.
- Classic facial phenotype.
- Asymmetry.
- Low birth weight (< -2DS).
- Feeding difficulties during infancy and early childhood.
- Tendency for fasting hypoglycemia.
- Developmental delay.
- Poor head control during infancy.
- Motor impairment caused by lack of muscle bulk and strength.
- Impairment of cognitive abilities (language, arithmetics) during childhood in 50% of cases (23).

The examinations that you can do for a case that you have suspicion for SRS are:

- Blood sugar.
- Bone age testing.
- Chromosome testing.
- Growth hormone exploration.
- Skeletal survey, to rule out other conditions that may mimic SRS.

Treatments that are recommended for these kind of children are:

- Growth hormone therapy can help if this hormone is lacking.
- High calories diet, to prevent low blood sugar.
- Physical therapy to improve muscle tone.
- Special education for children with disabilities and attention deficit problems.

These patients with Silver-Russell Syndrome, can be followed by a team of specialist like:

- A doctor specialized in genetics, can help diagnose Silver-Russell Syndrome.
- An endocrinologist may follow him with GH treatments, if it is needed.
- A gastroenterologist or a nutritionist can help him recommending the proper diet to enhance growth.
- Genetic counselors and psychologists may also be involved.

Our case has a classical form of SRS, with low birth weight, failure to thrive and a severe deficit of weight and height in the moment of diagnosis, body assimetry, relatively big head, triange-shape face, micrognatia, clinodactilia of the fifth finger of both hands.

The deficit of our patient's weight that is consistent and difficult to be corrected was perhaps, because of his limited diet at home or the specific type of genetic disorder of him. And this weight deficit also did not help him to have a better growth velocity during his treatment with GH.

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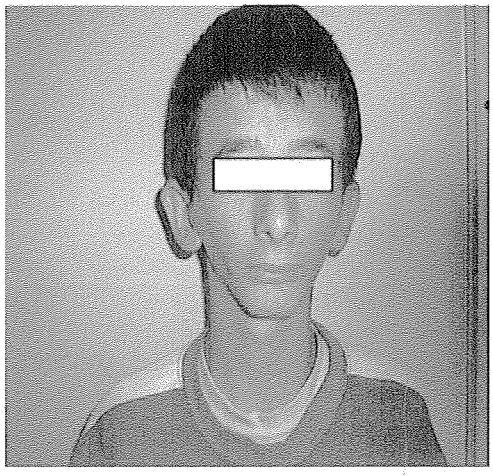

Fig.1. Child with SRS. See the asymmethry of the body, with the right side shorter and thinner, then the left side

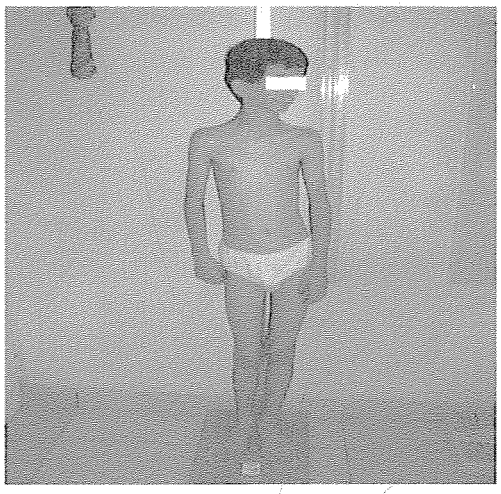

Fig. 2. The same child. See a small and triangle-looking face with expressed micrognatia, big ears in a relatively low position and a big nose

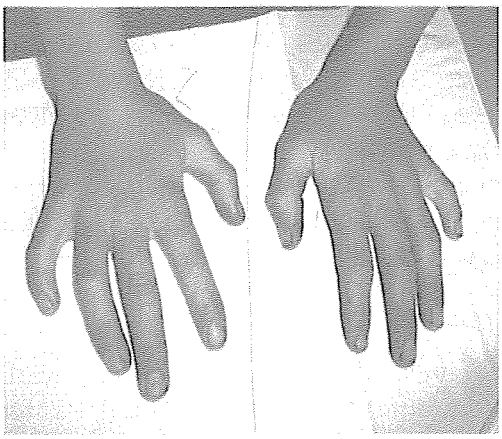

Fig.3. F.B. Clinodactilia of the 5th fingers (both hands)

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