Silver Russell Syndrome (SRS): a cause of partial IGF-I insensitivity ?

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BACKGROUND

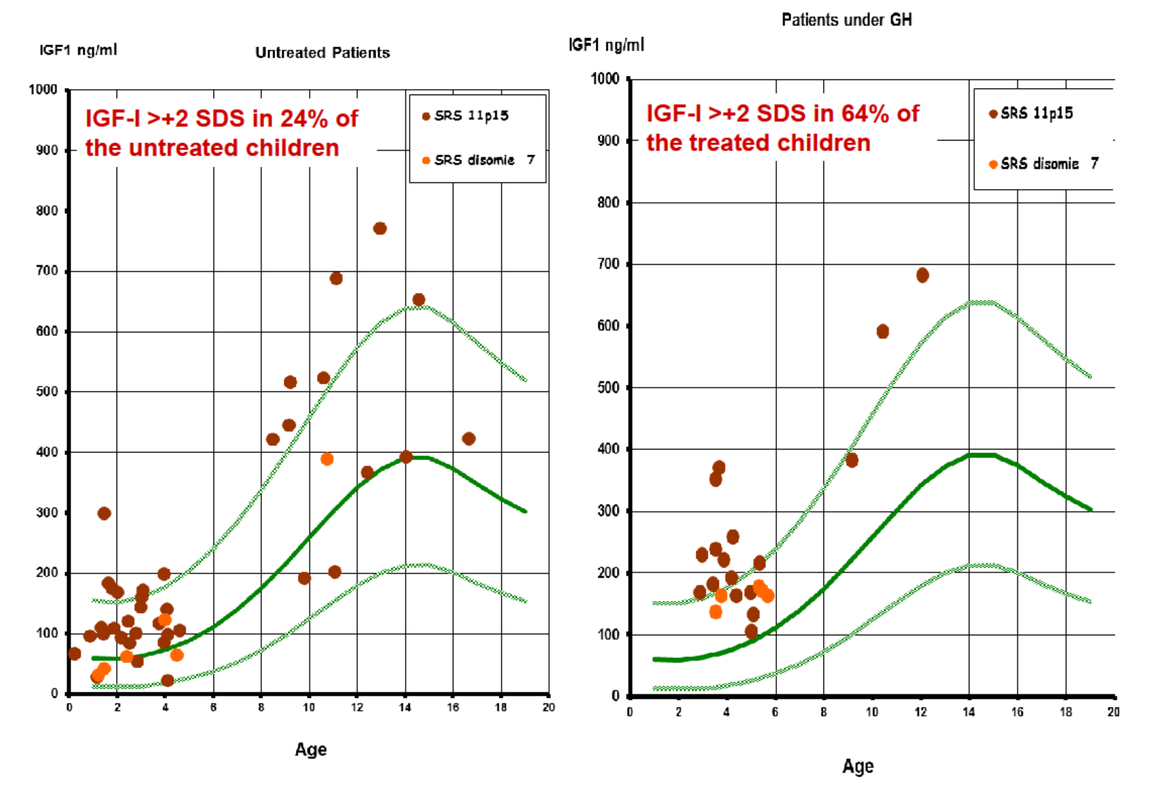
Silver-Russell syndrome (SRS) is characterized by intrauterine and postnatal growth retardation, relative macrocephaly at birth, prominent forehead, severe feeding difficulties and body asymmetry. In around 50%, it is secondary to hypomethylation at the IGF2/H19 imprinted locus on 11p15 (11p15 ICR1 LOM), and in 10% to a maternal disomy of chromosome 7 (mUPD7). Mechanisms of postnatal growth failure in SRS are not well understood.

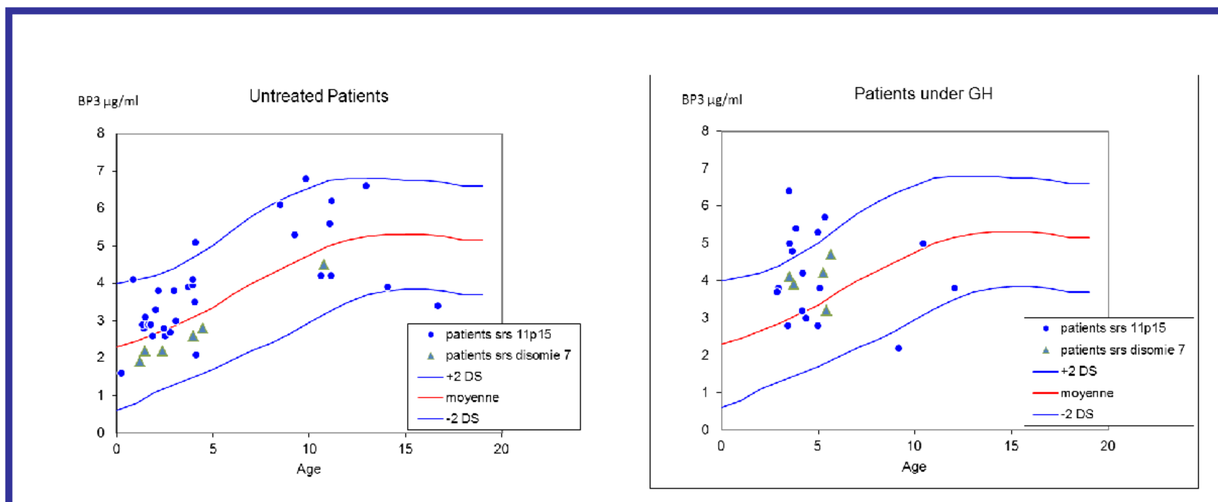
SRS diagnosis is supported by a clinical scoring system: (1) small for gestational age, birth length and/or weight ≤-2SDS, (2) postnatal growth retardation (height ≤-2SDS), (3) relative macrocephaly at birth, (4) body asymmetry, (5) feeding difficulties and/or body mass index (BMI) ≤-2SDS in toddlers, (6) protruding forehead at the age of 1-3 years. Subjects were considered to have likely SRS if they met at least four of these six criteria.

OBJECTIVES and METHODS

IGF-I and IGFBP-3 serum levels were documented in SRS without and with GH therapy. IGF-I and IGFBP-3 serum levels were measured by IRMA (kit IGF1-RIACT Cis-Bio assays, analytical sensitivity 1 ng/ml, intra assay coefficient 3,2% to 3,8%, inter assay 3,8 to 8,2%) and RIA (kit BP3 DSL-6600, analytical sensitivity 0,2 µg/ml, intra assay coefficient < 4,4%, inter assay coefficient < 13,5%) respectively in SRS children without (n=45) and after one year of GH treatment (n=22). Age related references (n= 660 blood samples of healthy children) were used to calculate standard deviation scores (SDS).

RESULTS





The median age before treatment was 3.9 yrs and median height -3 SDS. The median 1 year growth response to GH (median dose 31 µg/kg/day), expressed as the change in height SDS score, was + 0.8 (range 0 to +1.4).

CONCLUSIONS

Basal levels of both IGF-I and IGFBP-3 are increased for some SRS with 11p15 LOM even before GH treatment and very frequently during GH treatment. IGF-I levels are more often elevated than IGFBP-3 levels. During the first year of GH, growth velocity increased but only modestly, however GH augmentation was limited by elevated IGF-I levels in most patients. This suggests that SRS patients with 11p15 LOM have a partial IGF-I insensitivity of unknown mechanism complicating thereby the management of GH therapy in this group of patients.

References

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