Lessons from a patient carrying both an 11p paternal duplication and 15q deletion, illustrating the roles of IGF-II and IGF1R in growth regulation

Frédéric Brioude1, Sandra Chantot-Bastaraud2, Sandra Whalen3, Irène Netchine4, Eloise Giabicani2

1 Explorations Fonctionnelles Endocriniennes, Hôpital Trousseau, Inserm UMRS_938, Sorbonne Université, Paris, France
2 Département de Génétique, UF de Génétique Chromosomique, Hôpital Trousseau, Paris, France
3 Département de Génétique Médicale, Hôpital Trousseau, Paris, France

Introduction

The 11p15 region contains the IGF2 gene, which is imprinted (expressed only from the paternal allele). Overexpression of IGF2 leads to Beckwith Wiedemann syndrome (BWS), whereas loss of expression of IGF2 leads to Silver Russell syndrome. IGF-II, as well as IGF-I, promotes growth through the activation of the IGF receptor type 1 (IGF1R), which is located at 15q26. IGF1R defects have been implicated for years as a cause of intrauterine growth retardation (IUGR) with microcephaly.

We report here a patient with postnatal growth retardation and a complex chromosomal rearrangement, including a distal 15q26.3-qter deletion, encompassing part of IGF1R, and a mosaic paternal duplication of the entire 11p15 region. Although the 11p duplication should have led to BWS, the patient presented with growth retardation, microcephaly, and intellectual disability, which is in accordance with the IGF1R disruption phenotype.

Clinical presentation

The patient was born after 36 weeks of amenorrhea with normal birth weight (2380 g, -0.6 SDS) and microcephaly (head circumference 30 cm, -2.4 SDS). Target height was 159.5 cm (-0.7 SDS).

She presented with an early delay in language and cognitive development, strabismus, short stature and microcephaly.

Biology

At 3 years, IGF-I level was in the upper range of the norm (145 ng/ml, +0.9 SDS) with elevated basal GH (45 mU/L).

At 8 years, IGF-I level was high (345ng/ml, +2.1 SDS), with normal IGFBP-3 and a high level of ALS. This aspect is evocative of IGF1 resistance. Serum IGF-II was normal.

Genetic aspects

Karyotype: mosaic of
- 45,XX with a dicentric chromosome dic (15;21) and
- 46,XX cell line

SNP arrays:
- no copy number variation of chromosome 21
- a 15qter deletion, including a part of IGF1R (A)
- a 30% mosaic 11pter duplication, including IGF2 (B)

FISH analyses: mosaic of
- unbalanced translocation t(11p;15q) resulting in 11p duplication and 15q deletion (1)
- 20%: unbalanced translocation t(15q;21q) resulting in 15q deletion (2)
- 50%: 15q deletion (3)

Discussion/Conclusion

IGF1R defects are usually associated with IUGR with microcephaly. We hypothesize that the overexpression of IGF2 (due to the duplication of 11p) compensates the IGF1R defect during fetal life, leading to normal birth parameters in this patient. In this case, IGF-II may signal through a pathway that is independent from IGF1R during fetal life.

After birth, the patient presented with short stature. This suggests that the IGF1R defect prevails over IGF-II overexpression, which favors a predominant role of IGF-II in fetal rather than in postnatal growth.