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## OBJECTIVES

We describe the case of a young girl with a congenital malformations syndrome, hypogonadotropic hypogonadism and impaired bone quality associated with supernumerary markers at karyotype and chromosome 2 duplication.

Patients with supernumerary markers are very rare in literature: we aim to describe one of these cases in order to help genotype-phenotype correlation.

## CASE PRESENTATION

The proposita was born at 37<sup>th</sup> weeks of gestation from a twin pregnancy with a cesarean delivery presenting low birth weight for gestational age. She showed an aneurysm of the Galeno vein, a severe psychomotor delay, hiatal hernia, vernal keratoconjunctivitis and paroxysmal supraventricular tachycardia. The proposita also showed microcephaly, triangular face, synophrys, short philtrum, micrognathia, thoraco-lumbar scoliosis and a severe growth failure.

At the age of 17 years and 9 month, she was evaluated for delayed puberty and primary amenorrhea. Tanner stage was B3 PH4 AH3. GnRH stimulation test revealed hypogonadotropic hypogonadism (LH peak 5,67 mIU/mL). Oestrogen levels was very low, as well as inhibin B and anti-Mullerian factor levels. The pelvic ultrasound showed normal uterus and ovaries with reduced volume. Furthermore, blood tests showed vitamin D deficiency, a low total and ionized calcium levels and a high level of parathyroid hormone. The ultrasound bone densitometry revealed a very low bone mineral status (Z-score corrected for height = -3,8 SDS). The patient have spontaneous menarche at 18 years with secondary amenorrhea.



The karyotype showed the presence of three cell lines (7% with a normal female karyotype, 49% with one supernumerary marker and 44% with two supernumerary markers) and the molecular karyotyping performed by array-CGH highlighted a chromosome 2-pericentromeric duplication of approximately 14 Mbp (2p11.2 - 2q12.1).

## DISCUSSION

For the treatment of the secondary amenorrhea the proposita started estrogen therapy. This therapy also improved the bone status for which she has taken 1,25 OH vitamin D, calcium and magnesium supplementation and i.v. infusions of bisphosphonates.

Small supernumerary marker chromosomes (sSMCs) are found in 0.075 % of unselected prenatal cases, and in 0.044 % of postnatal cases, but frequencies are elevated to 0.125 % in infertile subjects and to 0.255 % in developmentally retarded patients. Approximately 30 % of markers are familial, while 70 % are de novo. The clinical phenotypes associated with marker chromosomes are also highly variable, from normal to severely abnormal. Besides, mosaicism is quite common, complicating genotype-phenotype correlation. Several mechanisms have been proposed to explain the formation of a *de novo* sSMC, including trisomy rescue (1)

Some sSMCs are associated with specific clinical disorders (+i(12)(p10) in Pallister-Killian syndrome), but for the majority of the other single sSMCs, a delineation of the relationship between genotype and clinical phenotype is a work in continuing progress. In literature there are few cases with a sSMC(2): the only correlation that has been postulated is that only those cases with markers that contain centromere-near sequences of 2p11.2 shows clinical abnormalities. Our patients confirm this hypothesis and our report of her characteristic gives further details to genotype-phenotype correlation.

## CONCLUSIONS

We suggest that this case may be a new congenital syndrome associated with severe psychomotor delay and hypogonadotropic hypogonadism. The pathogenetic role of specific genes in 2p11.2 - 2q12.1 region must be evaluated with further studies that involve genome analysis.

## References

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