

ATYPICAL PRESENTATION OF PRADER-WILLI SYNDROME WITH KLINEFELTER (XXY KARYOTYPE) AND CRANIOSYNOSTOSIS

Daniel R. Carvalho¹, Clovis S. Trad², João M. Pina-Neto³

ABSTRACT - Prader-Willi syndrome is a mental retardation genetic disorder also characterized by hypogonadism, hyperphagia and obesity. We report on a four-years-old boy, born to consanguineous parents, with uncommon co-occurrence of Prader-Willi syndrome, 47,XXY karyotype (Klinefelter syndrome) and coronal craniosynostosis. These are different unrelated conditions and it was not described before in the same patient to the best of our knowledge.

KEY WORDS: XXY karyotype, Prader-Willi syndrome, Klinefelter syndrome, craniosynostosis.

Síndrome de Prader-Willi em paciente com Klinefelter (cariótipo XXY) e craniossinostose

RESUMO - A síndrome de Prader-Willi é afecção genética de deficiência mental associada a hipogonadismo hipogonadotrófico, hiperfagia e obesidade. Descrevemos o caso de menino de 4 anos de idade, filho de casal consanguíneo, apresentando três condições clínicas não relacionadas: síndrome de Prader-Willi, cariótipo 47,XXY (compatível com síndrome de Klinefelter) e craniossinostose coronal. Ao nosso conhecimento, não foi relatado caso semelhante previamente na literatura.

PALAVRAS-CHAVE: cariótipo XXY, síndrome de Prader-Willi, síndrome de Klinefelter, craniossinostose.

Prader-Willi syndrome (PWS) is a genetic disorder with prevalence of 1/10,000 to 1/25,000 characterized by hypotonia in early infancy, hyperphagia, obesity and mental retardation in childhood associated with hypogonadism and short stature¹. Klinefelter syndrome (KS) is the most common sex chromosome disorder (1/500 male newborn) that usually is not easily clinical perceived during childhood and curses without developmental delay, but small testicles and infertility is a frequent problem in post-pubertal age². Several patients with both PWS and KS have been documented. The last reports revealed distinct genetic mechanisms of the two conditions that reinforce the coincidental association of (1) uniparental maternal heterodisomy of chromosome 15 and paternal X-Y chromosome non-disjunction³; or (2) paternally inherited microdeletion of chromosome 15 and maternal X-X inherited meiosis 1 non-disjunction^{4,5}.

Butler et al. solicited more reports of affected PWS patients with atypical presentation³. We describe another case of this co-occurrence of PWS and KS with the additional aspect of coronal craniosynostosis.

CASE

We have evaluated a four-years-old boy since his first year of life. He is the second child of a young consanguineous couple (F=1/16) and his sister had an isolated cleft lip. He was born after an uneventful pregnancy and vaginal delivery with a birth weight of 2,566 g and birth length of 46 cm.

At age 9 months, his length was 71 cm (25th percentile), his weight was 7.8 kg (3rd percentile), he had an OFC of 43.5 cm (between 3rd and 10th percentile), hypotonia, brachycephaly with pronounced temporal bossing, small penis (length of 2.1 cm, below 10th percentile) and cryptorchidia with hypoplastic scrotum. Peripheral blood cytogenetic analysis (GTG) at 550 band level resolution showed a 47,XXY karyotype. Bone reconstruction CT scan revealed an early closure of the anterior and posterior coronal sutures, but surgical intervention was not necessary (Figs 1, 2 and 3). Clinical observation noted obesity, hyperphagia and developmental delay without any sign of increased intracranial pressure. He sat at 18 months, crawled at 22 months and a broad-based flat-footed gait was observed at 3 years of age. At 4 years and 2 months of age, he had skin picking and was able to pronounce few words even after speech therapy. At this age, his length was 89 cm (below 3rd per-

Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto SP, Brazil: ¹Médico Residente do Serviço de Genética Médica; ²Professor Responsável pelo Centro de Ciências das Imagens e Física Médica; ³Professor Associado do Departamento de Genética.

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Dr. João Monteiro de Pina Neto - Setor de Genética Médica / Hospital das Clínicas de Ribeirão Preto - 14048-900 Ribeirão Preto SP - Brasil. E-mail: jmdpneto@fmrp.usp.br



Fig 1. Frontal view of the propositus at 1 year and 9 months of age.

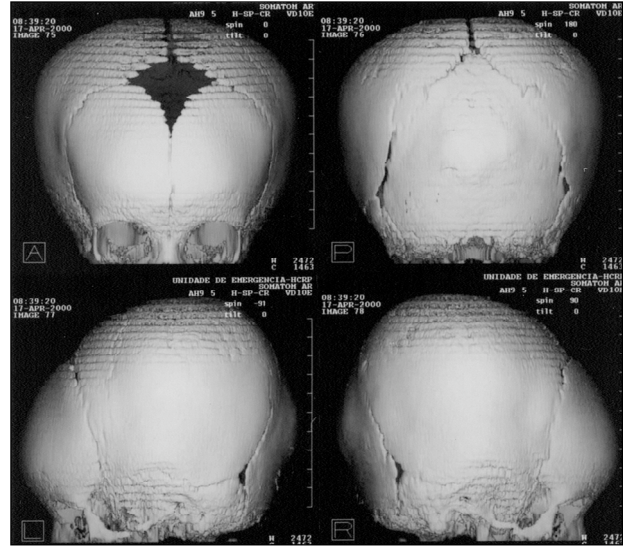


Fig 2. Bone reconstruction CT scan at 9 months of age showing an early closure of the anterior and posterior coronal sutures.

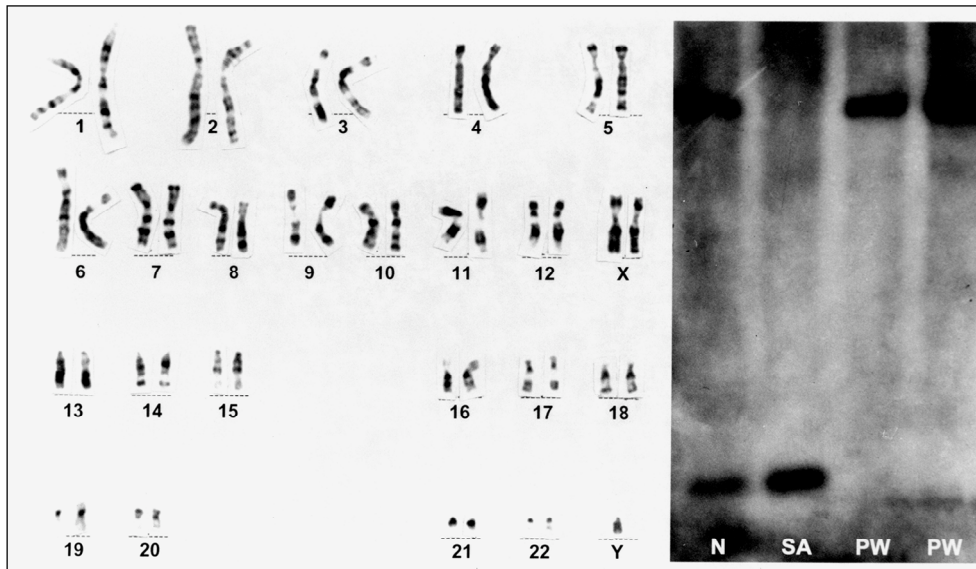


Fig 3. GTG banding karyotype with 47 chromosomes and XXY. Picture of southern blotting methylation test of 15q11-13 region using a KB17 probe for exon 1 of SNRPN gene, after DNA digestion with XbaI and NotI (methylation-sensitive restriction enzymes). N, normal pattern with a paternal derived 0.9 kb band and maternal derived 4.2 kb band; SA, pattern of Angelman syndrome with only a paternal derived band; PW (left), pattern of Prader-Willi syndrome with only a maternal derived band; PW (right), patient sample which is compatible with Prader-Willi syndrome.

centile), his weight was 18 kg (75th percentile), and he had an OFC of 48.5 cm (3rd percentile). Also observed was a narrow bifrontal diameter, epicanthic folds, almond shaped oblique palpebral fissures, esotropia, cupid arch upper lip with sticky saliva, marked truncal obesity and small hands and feet.

A methylation analysis was done by Southern blotting

using a KB17 probe to the 15q11-13 region that confirmed the missing paternal 0.9 Kb band compatible with PWS^{1,6} (Fig 3). Unfortunately, his mother died in an accident before the last exam. His grandmother became his legal guardian because his father moved away. It was not possible to investigate the parental origin of the genetic abnormality mechanism.

DISCUSSION

Craniosynostosis is considered a premature fusion of calvarial sutures, often associated with neurological manifestations or limb and craniofacial abnormalities. It can be an isolated clinical problem or part of diverse known syndromes⁷. The overall incidence for all forms of craniosynostosis is 1/2,000-1/2,500 live births⁷.

Considering the consanguinity and the absence of limb anomalies, we propose that non-surgical premature coronal closure may be a recessive, non-syndromic, form of craniosynostosis and also an incidental co-occurrence in this patient.

The clinical presentation of this case must be distinguished from non-synostotic posterior plagiocephaly (positional molding) secondary to hypotonia or sleeping in the supine position during the early perinatal period because anterior and posterior coronal sutures are involved bilaterally⁸.

Usually with the XXY boys, abnormalities are not apparent during childhood, except for possible mild language delays. Additionally, some authors reported that small penis and testes, or underdevelopment of external genitalia, are possible clues to precocious detection of Klinefelter children⁹, but these signs are found in few patients.

We believe that any uncommon aspect in XXY children – like hypotonia, hyperphagia, or the hypog-

onadism detected in our patient – should raise suspicion for evaluation of another associated condition. It would promote the early diagnosis that is essential for adequate management of PWS children.

Our report reinforces the importance of following affected children with any genetic disorder. The co-occurrence of these three unrelated different clinical problems in the same patient was not reported before.

REFERENCES

1. Pina-Neto JM, Ferraz VE, de Molfetta GA, Buxton J, Richards S, Malcolm S. Clinical-neurologic, cytogenetic and molecular aspects of the Prader-Willi and Angelman syndromes. *Arq Neuropsiquiatr* 1997;55: 199-208.
2. Smyth CM, Bremner WJ. Klinefelter syndrome. *Arch Intern Med* 1998;158:1309-1314.
3. Butler MG, Hedges LK, Rogan PK, Seip JR, Cassidy SB, Moeschler JB. Klinefelter and trisomy X syndromes in patients with Prader-Willi syndrome and uniparental maternal disomy of chromosome 15: a coincidence? *Am J Med Genet* 1997;72:111-114.
4. Geffroy S, Evrard V, Taufour D, Vanderbecken S, de Martinville B. Further example of a patient with Prader-Willi and Klinefelter syndromes of different parental origins. *Am J Med Genet* 1998;80:286-287.
5. Nowaczyk MJ, Zeesman S, Kam A, Taylor SA, Carter RF, Whelan DT. Boy with 47,XXY,del(15)(q11q13) karyotype and Prader-Willi syndrome: a new case and review of the literature. *Am J Med Genet* 2004; 125A:73-76.
6. Glenn CC, Saitoh S, Jong MT, et al. Gene structure, DNA methylation, and imprinted expression of the human SNRPN gene. *Am J Hum Genet*. 1996;58:335-346.
7. Cohen MM Jr, MacLean RE. *Craniosynostosis: diagnosis, evaluation and management*, 2nd edition. New York: Oxford University Press, 2000.
8. Ellenbogen RG, Gruss JS, Cunningham ML. Update on craniofacial surgery: the differential diagnosis of lambdoid synostosis/posterior plagiocephaly. *Clin Neurosurg* 2000;47:303-318.
9. Caldwell PD, Smith DW. The XXY (Klinefelter's) syndrome in childhood: detection and treatment. *J Pediatr* 1972; 80:250-258.