

chromosome Y. In most cases of XX male syndrome, translocation occurs in meiosis between chromosomes X and Y, and the SRY gene is located in chromosome X. However, this gene is not identified in other cases, in which several hypotheses have been proposed to explain male sex differentiation. This has been attributed to mutations in some of the more than 50 genes involved, in addition to sex chromosomes, in sex differentiation, or to Klinefelter syndrome (47, XXY) with subsequent loss of chromosome Y when virilization has already started.⁶

The SOX9 gene is a transcription factor essential for sexual and skeletal development, and its impairment may cause from bone changes alone to a combination of sex differentiation and skeletal abnormalities. Rearrangements have been reported in the SOX9 region, including duplication in the Xq 26 region, or balanced translocations *t*(17:20) (q24.3;q11.2) and *t*(7:17) (p13;q24), which have been associated to sex reversal and skeletal changes.^{7,8} The SOX3 gene shares the same functions as the SRY gene. Mutations causing changes or overexpression of this gene may induce male sex differentiation in individuals with 46, XX chromosomal endowment.⁹

Treatment of the XX male syndrome consists of repair surgery for gynecomastia, hypospadias, and cryptorchidism by testicular descent and orchiopexy, and even testicular prostheses. Prenatal diagnosis of these abnormalities is increasingly common.¹⁰

References

- De la Chapelle A. Analytic review: nature and origin of males with XX sex chromosomes. *Am J Hum Genet.* 1972;24:71–105.
- Audí Parera L, Gracia Bouthelie R, Castaño González L, Carrascosa Lezcana A, Barreiro Conde J, Bermúdez de la Vega JA, et al. Anomalías de la diferenciación sexual; protocolos diagnósticos-terapéuticos de la Asociación Española de Pediatría, 1; 2011. p. 1–12.
- Nistal M, García-Fernández E, Mariño-Enríquez A, Serrano A, Regadera J, González-Peramato P. Diagnostic value of the gonadal biopsy in the disorders of sex development. *Actas Urol Esp.* 2007;31:1056–75.
- Abusheikha N, Lass A, Brinsden P. XX males without SRY gene and with infertility. *Hum Reprod.* 2001;16:717–8.
- Audí L, Vicens-Calvet E. Desarrollo y diferenciación sexual normal. In: Argente Oliver J, Carrascosa Lezcana A, Gracia Bouthelie R, Rodríguez Hierro F, editors. *Tratado de Endocrinología Pediátrica y de la Adolescencia*. 2.ª ed. Madrid: DOYMA; 2000. p. 775–96.
- Pozo Román J, Argente Oliver J. Trastornos del desarrollo sexual. In: Pallardo Sánchez LF, Lucas Morante T, Marazuela Azpiroz M, Rovira Loscos A, editors. *Endocrinología clínica*. 2.ª ed. Madrid: Díaz de Santos; 2010. p. 176–89.
- Fonseca AC, Bonaldi A, Bertola DR, Kim CA, Otto PA, Vianna-Morgante AM. The clinical impact of chromosomal rearrangements with breakpoints upstream of the SOX9 gene: two novel de novo balanced translocations associated with acampomelic campomelic dysplasia. *BMC Med Genet.* 2013;14:50.
- Cox JJ, Willatt L, Homfray T, Woods CG. A SOX9 duplication and familial 46, XX developmental testicular disorder. *N Engl J Med.* 2011;364:91–3.
- Sutton E, Hughes J, White S, Sekido R, Tan J, Arboleda V, et al. Identification of SOX3 as an XX male sex reversal gene in mice and humans. *J Clin Invest.* 2011;121:328–41.
- Margarit E, Soler A, Carrió A, Oliva R, Costa D, Vendrell T, et al. Molecular, cytogenetic, and clinical characterisation of six XX males including one prenatal diagnosis. *J Med Genet.* 1998;35:727–30.

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Ketoacidosis as a debut to type 1B diabetes mellitus in a patient with Turner's syndrome[☆]



Cetoacidosis como inicio de diabetes mellitus tipo 1 B en una paciente con síndrome de Turner

In Turner syndrome (TS), mortality is three times higher as compared to the population with a normal karyotype.

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This is partly explained by the increasing incidence of diabetes mellitus (DM) and cardiovascular diseases.¹ There is an increased risk of developing both type 2 DM (relative risk, 4.4) and type 1 DM (DM1) (relative risk, 11.6) as compared to the general population.² Development of frank DM during childhood is however exceptional, and is usually more commonly associated to treatment with GH or sex hormones.^{2,3}

The unusual case of a two-year-old patient with DM1 of a non-autoimmune origin in whom TS was diagnosed is reported. Few patients with TS in whom DM1 has developed in childhood have been reported,^{3–6} and this is the youngest known.

Our patient was a Roumanian girl aged 2 years and 4 months with polyuria, polydipsia, and weight stagnation for the past two weeks. She weighed 8.100 kg (–3.6 SDS) and measured 77.5 cm in height (–3.8 SDS). The patient had a unique phenotype, with anteverted, low-set

pinnae, slight hypertelorism, and mandibular hypoplasia. Hyperglycemia (682 mg/dL) and metabolic acidosis (pH 7.13, pCO₂ 20 mmHg, HCO₃ 6.7 mmol/L, BE -20.6 mmol/L) were detected, which allowed for diagnosing diabetic ketoacidosis. Diabetes work-up was completed by measurement of HbA1c (11.1%) and C peptide (0.25 ng/mL; normal: 0.90–4 ng/mL), the latter by immunoluminescence. Tests for diabetes antibodies were requested (indirect immunofluorescence method: islet cell antibodies; radioisotopic method: insulin, glutamic acid decarboxylase, and tyrosine phosphatase antibodies) and they were all negative. There was no family history of autoimmune diseases. Type B DM1 was diagnosed based on the lack of evidence of autoimmunity.

Because of the unique features and low height, karyotype was requested and was found to be consistent with TS. A cytogenetic study of 15 metaphases was performed from a culture stimulated with phytohemagglutinin, with a resolution of 400 bands, and an isodicentric X chromosome with long arms was seen, which was confirmed by the band technique C: 46,X,psu idic(X)(p11.2)[15].

TS is associated to autoimmune conditions. Thus, when DM1 is diagnosed it appears logical to think that it is of the 1A type; however, some authors state that autoantibodies are more frequently negative in TS. This statement may however be conditioned by classification of DM based on the presence or absence of insulin dependence, which may lead to a wrong diagnosis of DM1 in patients with type 2 DM.^{3,7} On the other hand, some authors postulate the existence of mechanisms of destruction of pancreatic beta cells (PBCs) other than autoimmunity.²

Insulin deficiency secondary to PBC dysfunction and worsening with age has been reported in TS. At the earliest ages, this insulin deficiency is compensated by increased insulin sensitivity, but this would gradually decrease over time, which would lead to carbohydrate intolerance or even DM. Pathogenesis of this condition is independent from increases in body mass index and hypogonadism associated to TS, and is similar to pathogenesis of the mature-onset diabetes of the young (MODY), secondary to haploinsufficiency of some transcription factors affecting PBC function.⁴

A potential relationship has been seen between metabolic diseases and presence of an isochromosome of the long arm of the X chromosome (iXq).⁴ Schoemaker et al.¹ investigated causes of death in TS and found that in iXq karyotypes increased mortality was related to DM. It is hypothesized that there are genes in X chromosome involved in PBC function, and that haploinsufficiency of such genes could account for DM occurrence. This is also supported by the close similarity between type MODY diabetes and changes in carbohydrate metabolism in patients with TS.⁸ There are also studies reporting a greater prevalence of DM1 related to findings made in the short arm of the X chromosome (Xp). Bakalov et al.⁹ suggested that the greater incidence of DM in TS may be due to haploinsufficiency of genes located in chromosome Xp, so that DM incidence will be higher in patients with Xp monosomy (45X; delXp; iXq), with a normal incidence in long arm deletions (delXq), where both Xp arms are preserved. However, the greater incidence of DM in iXq patients may also be explained by overexpression of genes located in chromosome Xq which would escape inactivation, and which would be related to PBC function,

and to another series of systemic processes which would promote a pro-inflammatory state. These statements are supported by a study conducted in 2008 showing a higher mortality rate in iXq patients,¹ and by the fact that there is also a greater incidence of DM in patients with Klinefelter syndrome (47XXY) and in 48 XXYY patients, in whom there are supernumerary copies of Xq.¹⁰

Association of TS and DM1 may actually be due to mechanisms inherent to chromosomal findings. Association of TS to autoimmunity is however widely known, and a potential, currently undetectable autoimmune basis cannot therefore be ruled out with full certainty. Regular autoantibody monitoring is therefore recommended.

Association of DM to genetic syndromes provides unique information for studying the genetic cases of carbohydrate metabolism. There is still a long road ahead before knowing the pathophysiological and genetic bases justifying DM1 occurrence in TS. New advances in genetic testing, as well as creation of multicenter databases, will allow for more complete understanding of this syndrome and PBC pathophysiology.

Conflict of interest

The authors state that they have no conflicts of interest.

References

1. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Mortality in women with Turner syndrome in great Britain: a national cohort study. *J Clin Endocrinol Metab.* 2008;93:4735–42.
2. Gravholt CH. Epidemiological, endocrine and metabolic features in Turner syndrome. *Arq Bras Endocrinol Metabol.* 2005;49:145–56.
3. Elsheikh M, Dunger DB, Conway GS, Wass JAH. Turner's syndrome in adulthood. *Endocr Rev.* 2002;23:120–40.
4. Bakalov VK, Cooley MM, Quon MJ, Luo ML, Yanovski JA, Nelson LM, et al. Impaired insulin secretion in the Turner metabolic syndrome. *J Clin Endocrinol Metab.* 2004;89:3516–20.
5. Terano T, Fukuda K, Nakamura M, Takiguchi Y, Sakai Y, Hirai A. Diabetic ketoacidosis with recurrent pulmonary edema and rhabdomyolysis in a patient with Turner's syndrome. *Intern Med.* 2001;40:418–20.
6. Gonc EN, Ozon A, Alikasifoglu A, Kandemir N. Type 1 diabetes mellitus in a 3½ year-old girl with Turner's syndrome. *J Pediatr Endocrinol Metab.* 2002;15:1203–6.
7. Gravholt GH, Juul S, Naeraa RW, Hansens J. Morbidity in Turner syndrome. *J Clin Epidemiol.* 1998;51:147–58.
8. Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Mosekilde L, Bennett P, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care.* 2006;29:1591–8.
9. Bakalov VK, Chenh C, Zhou J, Bondy A. X-chromosome gene dosage and the risk of diabetes in Turner syndrome. *J Clin Endocrinol Metab.* 2009;94:3289–96.
10. Pankowska E, Szalecki M, Romer TE. Metabolic control and insulin administration in a girl with turner syndrome and type 1 diabetes during long-term growth hormone therapy. *Pediatr Endocrinol Diabetes Metab.* 2007;13:213–5.

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