Rev Med Int Sindr Down. 2016;**20(2)**:21–24

FUNDACIÓ CATALANA SÍNDROME DE DOWN
www.fcsd.org

INTERNATIONAL MEDICAL REVIEW ON DOWN'S SYNDROME

www.elsevier.es/sd

CASE REPORT

Association of Down syndrome and tuberous sclerosis and their similarities in m-TOR pathway overactivation. About a case

D.A. Echeverry Rivera[a,b,*], **F. Ariza Cadena**[a,b,c]

[a] *Facultad de Ciencias de la Salud, Universidad ICESI, Cali, Colombia*
[b] *Fundación Clínica Valle del Lili, Cali, Colombia*
[c] *Member of the Sociedad Colombiana de Anestesiología, Colombia*

Received 16 May 2015; accepted 21 April 2016
Available online 18 June 2016

KEYWORDS
Down syndrome;
Tuberous sclerosis;
Neurocutaneous;
Trisomy 21;
m-TOR

Abstract
Background: The association between Down syndrome and Tuberous sclerosis (DS/TSC) has very rarely been described. These two entities present in common overactivation of the m-TOR system (mammalian rapamycin ligand), which has been related to abnormal neuronal growth, abnormal synaptic transduction and neurotransmitter overstimulation in different brain areas (among others) that result in cognitive retardation and autistic symptoms.
Case summary: We present a girl with a diagnosis of DS, with early childhood onset presenting convulsive tonic-clonic seizures and hypopigmented skin plaques. A brain MRI revealed cortical tubers suggestive of TSC. A subsequent echocardiogram showed the presence of multiple endomyocardial lesions suggestive of rhabdomyoma. Further follow-ups showed spontaneous resolution of these cardiac lesions, but persistence of brain disorders. We also describe the refractoriness of the convulsive events despite appropriate treatment with multiple anticonvulsants.
Conclusions: Neurological and cardiac implications in patients with DS/TSC association lead to a difficult therapeutic scenario with a high rate of complications, partially due to symptomatic refractoriness. New drugs aimed at the m-TOR signalling pathway could be very useful in this picture, given its relationship to improvement of cognitive impairment and tumours associated with these two entities.

* Corresponding author.
E-mail address: diegoecheverry03@hotmail.com (D.A. Echeverry Rivera).

http://dx.doi.org/10.1016/j.sdeng.2016.04.001

PALABRAS CLAVE
Síndrome de Down;
Esclerosis tuberosa;
Neurocutáneos;
Trisomía 21;
m-TOR

Asociación síndrome de Down-esclerosis tuberosa y sus similitudes en la sobreactivación de las vías m-TOR. A propósito de un caso

Resumen
Antecedentes: La asociación entre síndrome de Down y esclerosis tuberosa (SD/ET) muy pocas veces ha sido descrita. Estas dos entidades presentan en común una sobreactivación del sistema m-TOR (ligando para rapamicina mamífero-específico), cosa que se ha visto relacionada con crecimiento neuronal anómalo, transducción sináptica anómala y sobreestimulación de neurotransmisores en diferentes áreas cerebrales, entre otras, que se manifiestan en retardo cognitivo y síntomas autistas en los pacientes en quienes se presentan.
Resumen del caso: Presentamos una niña con diagnóstico de SD quien debutó a temprana edad con crisis convulsivas tónico-clónicas y placas hipopigmentadas en piel. Se tomó una resonancia cerebral la cual reportó imágenes de túberes corticales sugestivas de ET. Un ecocardiograma posterior evidenció la presencia de múltiples lesiones endomiocárdicas sugestivas de rabdomiomas. Controles ulteriores mostraron resolución espontánea de estas lesiones cardiacas, pero con persistencia de las alteraciones cerebrales. Se describe la refractariedad de los episodios convulsivos a pesar de tratamiento apropiado con múltiples anticonvulsivantes.
Conclusiones: Las implicaciones neurológicas y cardiacas en pacientes con asociación SD/ET ocupan un escenario terapéutico difícil con alta tasa de complicaciones, en parte debidas a la refractariedad sintomática. Los nuevos medicamentos dirigidos hacia la vía de señalización m-TOR podrían ser de gran utilidad en este escenario, dada su relación con mejoría del deterioro cognitivo y tumoraciones asociadas a estas dos entidades.

Introduction

Down syndrome (DS) is considered the main principal cause of chromosome-generated intellectual disability,[1,2] with a prevalence of 1:150 conceptions and 1:3000 live newborns, mostly due to the fact that these fecundations are unviable. In turn, tuberous sclerosis (TSC) is characterized by autosomal dominant transmission and the inactivation of the TSC1 and/or TCS2 genes (chromosomes 9 and 16),[3] which code for the hamartin and tuberin proteins respectively. The condition presents a prevalence de 1:10,000 births; it falls within the framework of neurocutaneous syndromes,[4] affecting the skin and the central nervous system (CNS) with sebaceous adenomas, hypopigmented maculae, Koenen periungueal fibromas, angiomyolipomas, cortical tubers, subependymal nodules and cardiac rhabdomyomas, among others.[5]

Concomitant DS/TSC has very rarely been reported. Previous studies have suggested that these syndromes have no causal or clinical relationship and that this presentation is the product of the prevalence of each condition separately (1:30,000,000 births).[6,7] Consequently, it would be of interest to ascertain the details of the clinical behaviour of this association and whether there are similarities in the specific molecular pathways that can suggest shared genetic and molecular patterns, as in the case of the m-TOR signalling pathway. This route is overexpressed in these patients and generates anomalous cell growth and cognitive deterioration, as will be discussed further later in the article.

Clinical case

We present the case of a female born at the gestational age of 8 months, with karyotype and features confirming DS (47,XX,+21; normal karyotype in the parents), without relevant gestational antecedents. Echocardiogram revealed a restrictive permeable foramen ovale with at least 3 intramyocardial tumours of an average of 5 × 5 mm in the ventricular walls and intraventricular septum compatible with rhabdomyomas, lacking haemodynamic compromise. Due to the association between cardiac rhabdomyomas and TSC, a computed tomography (CT) scan of the brain was performed. This showed dense images in the subcortical and subependymal white matter, corresponding to cortical tubers. Contrast cranial nuclear magnetic resonance (NMR) spectroscopy revealed multiple subependymal lesions (Figs. 1–3) suggestive of cortical nodules and subependymal tubers, with signs of volume loss in the posterior fossa (Fig. 4).

Weeks later, the patient presented with repetitive tonic-clonic seizures hard to control with the initial management; the first electroencephalogram revealed right temporal-central-frontal epileptiform activity. In a later assessment (at the age of 2 years) multiple hypopigmented/hypochromic patches on the trunk and patent hypothyroidism were found. The patient remained cardiovascularly asymptomatic and posterior echocardiogram follow-ups revealed that the foramen ovale persisted, with spontaneous resolution of the intracardiac lesions (at the age of 4 years); at that time she was found to show height and weight lag (height 92 cm; weight 13.6 kg) and intense psychomotor developmental delay (crawling and sitting with help; guttural sounds).

When this article was prepared (patient age of 5 years), treatment with multiple anticonvulsant thyroid supplementation continued, without true control of the convulsions. Over the last 2 years, she presented repeated lung symptoms that made it necessary to be admitted to hospital.