CEREBELLO-TRIGEMINAL DERMAL DYSPLASIA (GOMEZ-LOPEZ-HERNANDEZ SYNDROME)

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Introduction

Cerebello-trigeminal dermal (CTD) dysplasia (OMIM # 601853) (OMIM 2006) is an uncommon congenital disorder of the cerebellum, trigeminal nerves, cranial sutures and scalp (Muñoz et al. 2004). Clinically, CTD dysplasia is characterised by craniosynostosis, parieto-occipital scalp alopecia, trigeminal nerve anaesthesia, short stature, cerebellar abnormalities (usually of the rhombencephalosynapsis/RES type), ataxia and intellectual impairment (Brocks et al. 2000; Gomez 1979, 1987; Gomy et al. 2008; Lopez-Hernandez 1982; Munoz et al. 1997, 2004; Pascual-Castroviejo 1983; Poretti et al. 2008; Schell-Apacik et al. 2007; Tan et al. 2005).

Historical background and eponyms

The first four cases of CTD dysplasia were reported by Gomez (1979), Lopez-Hernandez (1982) and Pascual-Castroviejo (1983). The condition is also known as *Gomez-Lopez-Hernandez syndrome*. All the first four patients had the same clinical manifestations (see below), including scarring from self-inflicted injuries, belonged to different families and only two were from the same country (Gomez 1987). Some cases in the earlier German literature could correspond to CTD dysplasia (Kayser 1921, Gross 1959, Pillat 1949). Kayser (1921) reported a boy with bilateral congenital corneal anaesthesia and difficult swallowing and chewing who was unable to stand or walk and who died of pneumonia at age 3.6 years (Gomez 1987). Pillat (1949) reported a patient with congenital trigeminal anaesthesia and symmetrical hypoplasia of the hair and part of the temporal muscles with no apparent ataxia (Gomez 1987). Gross (1959) reported mental retardation, strabismus, hypertelorism and turricephaly in two patients with RES (Muñoz et al. 2004). Further cases who could have CTD dysplasia may have been reported as syndrome RES (Pavone et al. 2005, Toelle et al. 2003, Muñoz et al. 2004) because of abnormal corneal sensation (Truwit et al. 1991) or craniofacial abnormalities (Pavone et al. 2005, Toelle et al. 2003). For this and other reasons (see below) isolated RES and CTD dysplasia are currently (putatively) considered as a spectrum of disease with common aetiology (Tan et al. 2005).

Incidence and prevalence

Twenty patients have been identified with true CTD dysplasia since 1979 (Alonso, personal communication; Bowdin et al. 2007; Brocks et al. 2000; Gomez 1979, 1987; Gomy et al. 2008; Lopez-Hernandez 1982; Muñoz et al. 1997, 2004; Pascual-Castroviejo 1983; Poretti et al. 2008; Purvis et al. 2007; Schell-Apacik et al. 2008; Tan et al. 2005; Whetsell et al. 2006). It remains unclear how many cases with RES (Pavone et al. 2005, Toelle et al. 2003) could be considered part of the CTD dysplasia spectrum (Tan et al. 2005). CTD dysplasia seems to be sporadic and all patients reported to date belong to unrelated families.

Clinical features

The patients with CTD dysplasia show, since birth, acrocephaly with occipital flattening, moderate hypertelorism and convergent strabismus, symmetrical areas of alopecia involving the lateral skull that commonly extend to the parietal areas, but also can affect tempo-

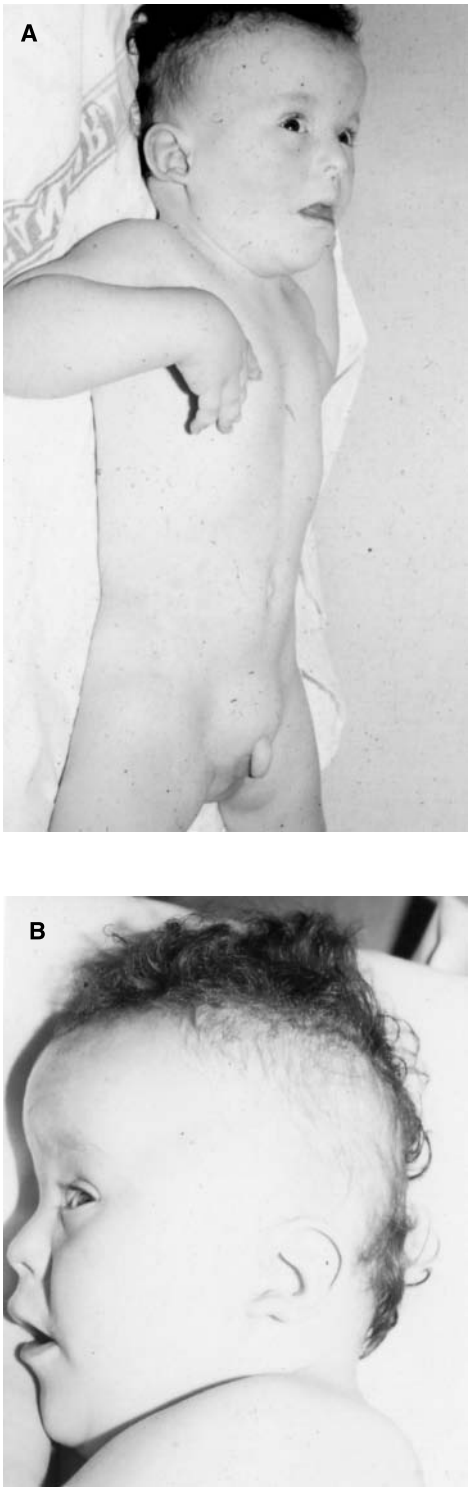

Fig. 1. Cerebellar trigemino dermal dysplasia. General (**A**) and lateral head and face views (**B**) show acrocephaly, open mouth, short nose, and alopecia in the parietal region of scalp.

ral and occipital regions (Fig. 1), varying degrees of bilateral trigeminal anaesthesia confirmed by EMG studies which show very prolonged latencies on R2 bilaterally and may identify an afferent lesion involving also the blink reflex (Muñoz et al. 1997, 2004).

Most patients show characteristics facial abnormalities including frontal bossing, flat occiput, hypertelorism, small nose with broad base and bulbous tip, apparently low-set and posteriorly angulated ears, thin lips and open mouth most of the time, prognatism, dental malocclusion, deciduous teeth eruption and dental abnormalities, high palate, and corneal opacities due to lack of pain sensation and to self-injuries. They all have clinodactyly of the fifth fingers and also have feeding difficulties because of masseter and temporal muscle weakness (Muñoz et al. 2004). In a male patient Brocks et al. (2000) recorded growth hormone deficiency.

Skin biopsy from areas of alopecia shows a decreased number of hair follicles (Lopez-Hernandez 1992, Muñoz et al. 1997), but preserved architecture although undeveloped head-sebaceous structures.

Postnatal motor development occurs with short stature, ataxia seizures motor and mental delay, hyperactivity and behavioural disorders. Unaided walking was obtained at age 19 months (Alonso L.G., personal communication), 2.9 years (Brocks et al. 2000), 4 years (Muñoz et al. 1997), after 5 years (Gomez 1979), and at 7 years (Lopez-hernandez 1982, Muñoz et al. 1997). In two cases there was no intellectual impairment (Alonso L.G., personal communication).

The longest follow-ups so far recorded were those of Brocks et al. (2000) in a 19 year old male followed since birth who was of short stature and showed signs of progression of his physical and psychiatric problems including hyperactivity, depression, self-injurious behaviour and bipolar disorders; and Gomy et al. (2008) in a 29-year-old patient. Mental problems and behavioural disorders in the other cases followed-up for long periods (i.e., to puberty) tended to improve with age and patients became more sociable (Muñoz et al. 1997).

Radiographic findings

Skull X-ray studies shows brachicephaly with tower-like shape, reduced posterior fossa volume, and

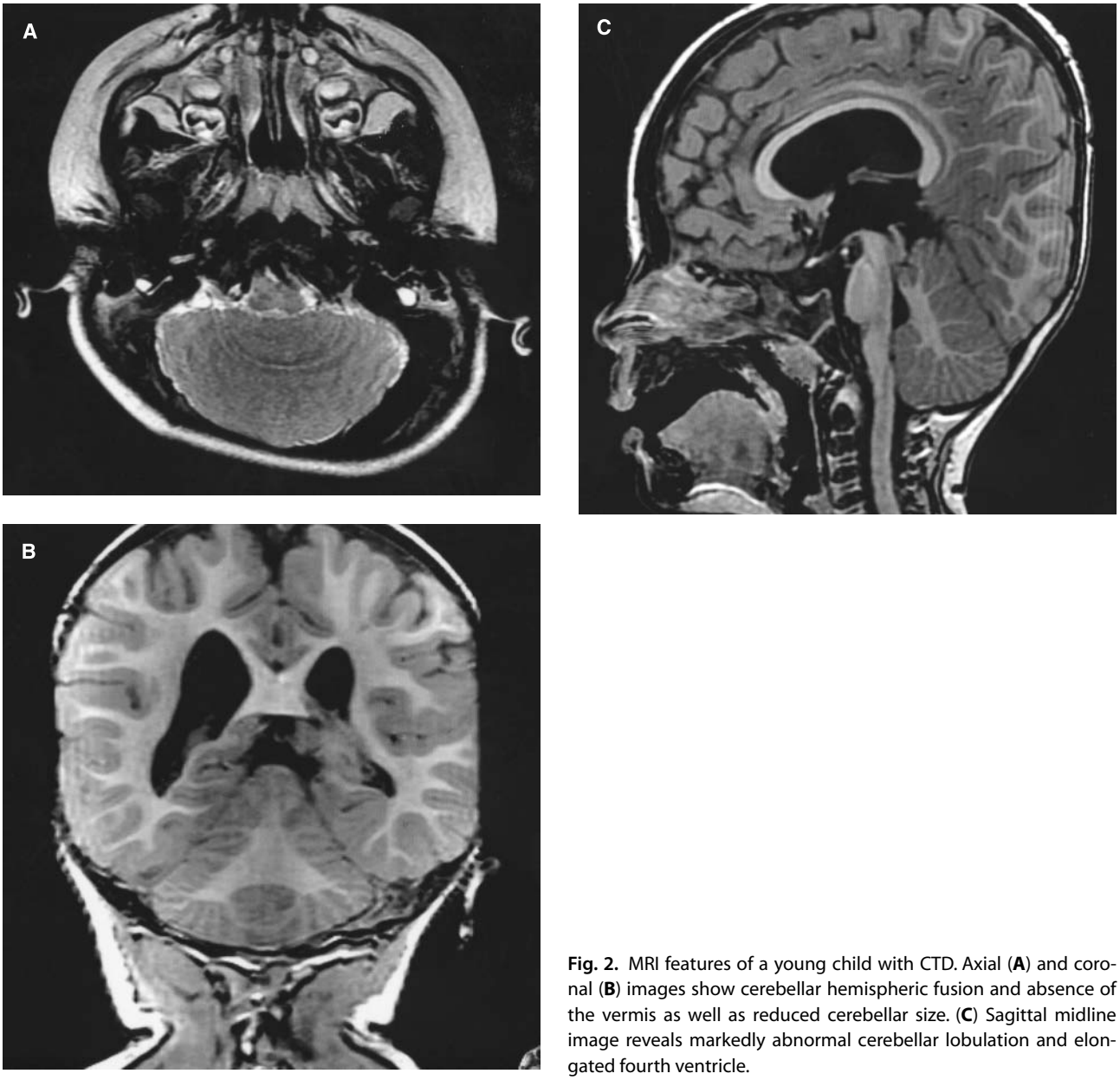

Fig. 2. MRI features of a young child with CTD. Axial (**A**) and coronal (**B**) images show cerebellar hemispheric fusion and absence of the vermis as well as reduced cerebellar size. (**C**) Sagittal midline image reveals markedly abnormal cerebellar lobulation and elongated fourth ventricle.

craniosynostosis with partial closure of the lambdoid sutures.

Cerebellar hypoplasia and fusion of the vermis and pons was demonstrated by Lopez-Hernandez (1982) on CT studies. MRI studies reveal RES (Brocks et al. 2000, Muñoz et al. 1997), a rare malformation that is characterized by fusion of cerebellar hemispheres and absence of the cerebellar vermis (Fig. 2). The associated central nervous system anomalies most commonly present are fusion of the cerebellar dentate nuclei, superior cerebellar peduncles, and thalami, absence of the septum pellucidum, olivary hypoplasia, anomalies of the limbic system, hydrocephalus and azygons anterior cerebral artery (Gomy et al. 2008, Tan et al. 2005, Truwit et al. 1991, Whetsell et al. 2006). The presence of associated supratentorial lesions is a more likely cause of severe mental disease than the malformations of the

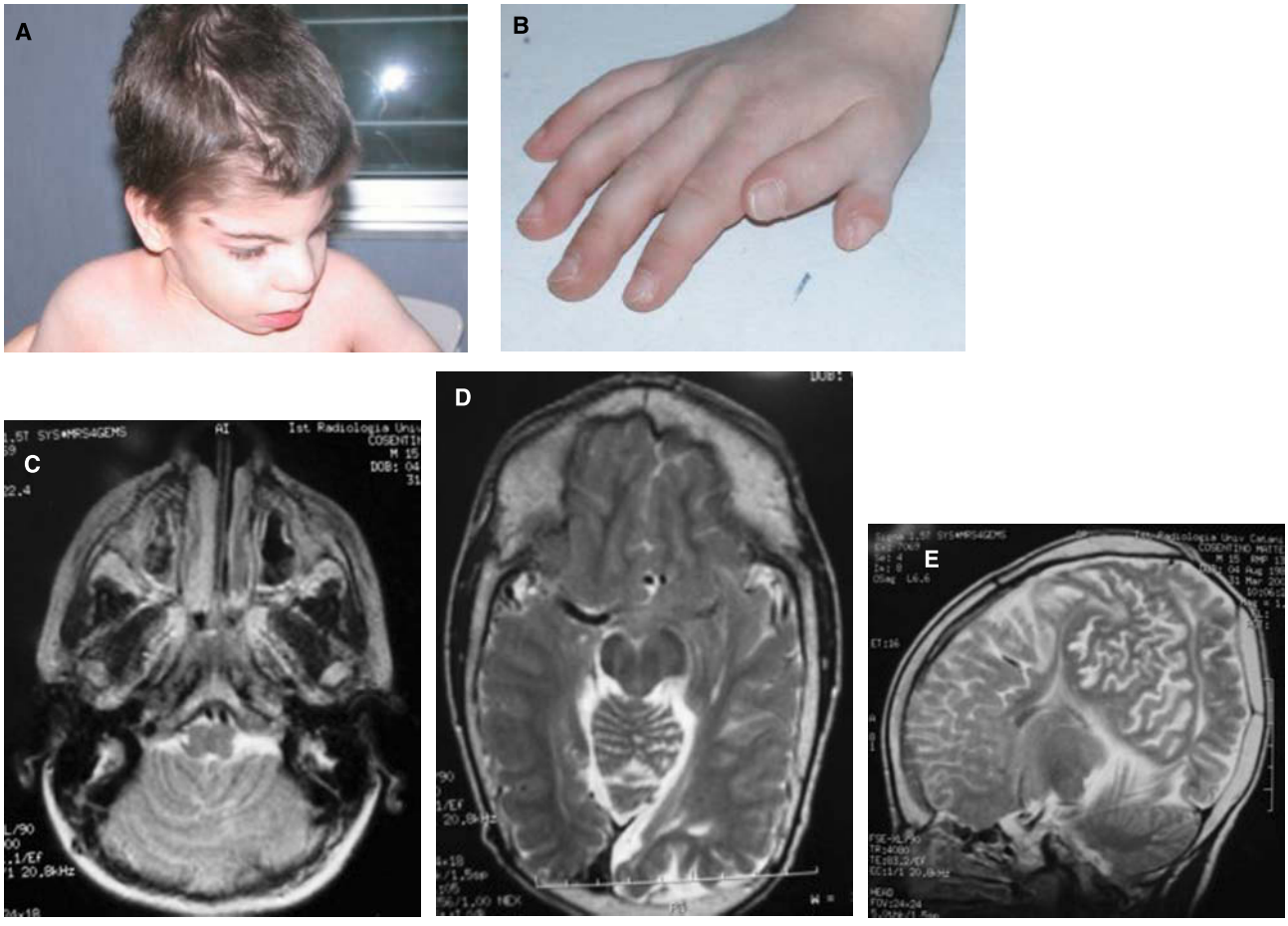

Fig. 3. A child with a complex malformation syndrome fitting in the group of the rhombenecephalosynapsis (RES) who have clinical features similar to CTD dysplasia: (**A**) cutis vertex rigirata with an area of alopecia in the right fronto-parietal area and a tuft of hair in the outer region of the right eyebrow; (**B**) hexadactylu with thumb duplication; and evidence of RES at axial (**C**, **D**) and sagittal (**E**) MRI study of the brain (reprinted with permission from Pavone et al. 2005).

posterior fossa (Muñoz et al. 1997, 2004) however the overall CNS malformation is complex and thus is almost invariably associated to neurological manifestations. Prenatal MRI of RES in a CTD dysplasia infant who had an abnormally shaped small cerebellum at antenatal ultrasound has been recently published (Tan et al. 2005).

Pathogenesis

Pathogenesis of CTD dysplasia is not completely understood to date. The cerebellum develops late in the human embryo. The vermis is formed at 4 months of gestation, after the semilunar ganglion of the trigeminal nerve has been formed from migrating neural crest cells and thickened epidermis of each side of the head that formed placodes (Gómez 1987). In CTD dysplasia, the primordial cerebellar hemispheres, the placodes that give origin to the trigeminal nerve, and the epidermis of the occipito-parietal region that originates from the ectoderm, are affected. Failure of local epidermal development and of migration and multiplication of specific cells from a selective region in the ectoderm have been suggested as the cause of hypoplasia or dysplasia of the cerebellum, trigeminal nerves and a parieto-occipital segment of the scalp (Gomez 1987). The biology of RES is not

completely understood, but the rarity of this cerebellar malformation, which seems likely to be universally present in CTD dysplasia patients, suggests that it is one of the key features of this syndrome and that CTD dysplasia and isolated RES may have a common aetiology (Tan et al. 2005) (see also Fig. 3).

In a recent report (Schell-Apacik et al. 2008) microarrary-based comparative genomic hybridisation (array-CGH) revealed chromosomal observations including partial deletions of 1p21, 8q24.23, 10q11.2, Xq26.3 and partial duplications of 19p13.2 which, however, were classified as normal variants. Molecular analysis of the lysosomal acid phosphatase gene (ACP2) was performed by Gomy et al. (2008) with no pathogenic mutations.

Differential diagnosis

Clinical and imaging features of CTD are very particular and differential diagnosis with other syndromes is not frequent, especially after one year of age. Differential diagnosis may be necessary to identify some patients with ataxia or severe mental retardation who show self corneal injuries. Isolated (non syndromic) RES must be carefully evaluated for the presence of associated systemic malformations suggestive of CTD dysplasia (Pavone et al. 2005, Toelle et al. 2003, Tan et al. 2005).

Management

Treatment of CTD dysplasia is symptomatic and includes physical rehabilitation, special education, dental care, and ocular protection against self-induced corneal trauma that causes ulcers and, later, corneal opacification. Bilateral congenital trigeminal anaesthesia may require lifelong corneal protection.

The prognosis is related to the mental development, motor handicap, corneal-facial anaesthesia, and visual problems.

Follow-up of a large number of patients with CTD has not been reported in the literature and experience is limited to few cases to date.

References

Bowdin S, Phelan E, Watson R, McCreery KM, Reardon W (2007) Rhombencephalosynapsis presenting antenatally with ventriculomegaly/hydrocephalus in a likely case of Gómez-López-Hernández syndrome. Clin Dysmorphol 16: 21–25.

Brocks D, Irons M, Sadeghi-Nadjad A, Mc Cauley R, Wheeler P (2000) Gómez-López-Hernández syndrome: expansion of the phenotype. Am J Med Genet 94: 405–408.

Gomez MR (1979) Cerebello-trigeminal and focal dermal dysplasia: a newly recognized neurocutaneous syndrome. Brain Dev 1: 253–256.

Gomez MR (1987) Cerebello-trigeminal-dermal dysplasia. In: Gomez MR (ed.) Neurocutaneous diseases. A practical approach. Stoneham: Butterworths, pp. 345–348.

Gomy I, Heck B, Santos AC, Figueiredo MS, Martinelli CE Jr, Nogueira MP, Pina-Neto JM (2008) Two new Brazilian patients with Gómez-López-Hernández syndrome: reviewing the expanded phenotype with molecular insights. Am J Med Genet A 146A: 649–657.

Gross H (1959) Die Rhombencephalosynapsis, eine systemisierte Kleinhirnfehlbildung. Arch Psychiatr Z Neurol 199: 537–552.

Kayser B (1921) Ein Fall von angeborener Trigeminuslähmung und angeborenem totalem Tränenmangel. Klin Mel Augenheilkd 66: 652–654.

Lopez-Hernandez A (1982) Craniosynostosis, ataxia, trigeminal anesthesia and parietal alopecia with pons-vermis fusion anomaly (atresia of the fourth ventricle). Report of two cases. Neuropediatrics 13: 99–102.

Muñoz MV, Santos AC, Graziadio C, Pina-Neto JM (1997) Cerebello-trigeminal-dermal dysplasia (Gómez-López-Hernández syndrome): Description of three new cases and review. Am J Med Genet 72: 34–39.

Muñoz Rojas MV, dos Santos AC, De Pina-Neto JM (2004) Cerebello-trigemino-dermal dysplasia. In: Roach ES, Miller VS (eds.) Neurocutaneous Disorders. Cambridge: Cambridge University Press, pp. 306–312.

OMIM™ (2006) Online mendelian inheritance in man. Baltimore: Johns Hopkins University. http://ncbi.nlm.nih.gov/omim

Pascual-Castroviejo I (1983) Displasia cerebelotrigeminal. Neurologia Infantil, Barcelona. Cientifico-medica: 680.

Pavone P, Incorpora G, Ruggieri M (2005) A complex brain malformation syndrome with rhombencephalosynapsis, preaxial hexadactyly plus facial and skull anomalies. Neuropediatrics 36: 279–283.

Pillat A (1949) Wiener ophthalmologische Gesellschaft. Epithelschädigung der Hornhaut bei angeborener Trigeminushypoplasie. Wien Klin Wochenschr 61: 605.

Poretti A, Bartholdi D, Gobara S, Alber FD, Boltshauser E (2008) Gómez-López-Hernández syndrome: an easily missed diagnosis. Eur J Med Genet 51: 197–208.

Purvis DJ, Ramirez A, Roberts N, Harper JI (2007) Gómez-López-Hernández syndrome: another consideration in focal congenital alopecia. Br J Dermatol 157: 196–198.

Schell-Apacik CC, Cohen M, Vojta S, Ertl-Wagner B, Klopocki E, Heinrich U, von Voss H (2008) Gomez-Lopez-Hernandez syndrome (cerebello-trigeminal-dermal dysplasia): description of an additional case and review of the literature. Eur J Pediatr 167: 23–26.

Tan TY, McGillivray G, Goergen SK, White SM (2005) Prenatal magnetic resonance imaging in Gómez-López-Hernández syndrome and review of the literature. Am J Med Genet 138A: 369–373.

Toelle SP, Valcinkaya C, Kocer N, Deonna T, Overweg-Plandsoen WCG, Bast T, Kalmanchey R, Barsi P, Schneider JFL, Capone Mori A, Boltshauser E (2003) Rhombencephalosynapsis: clinical findings and neuroimaging in 9 children. Neuropediatrics 33: 209–214.

Truwit CL, Barkovich AJ, Shanahan R, Maroldo TV (1991) MR imaging of rhombencephalosynapsis: report of three cases and review of the literature. Am J Neuroradiol 12: 957–965.

Whetsell W, Saigal G, Godinho S (2006) Gómez-López-Hernández syndrome. Pediatr Radiol 36: 552–554.