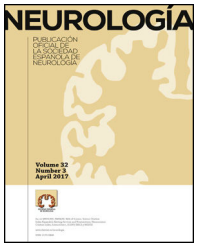
Neurología. 2020;35(3):207—221

SOCIEDAD ESPAÑOLA DE NEUROLOGIA

NEUROLOGÍA

www.elsevier.es/neurologia



LETTERS TO THE EDITOR

Expanding FOXG1 syndrome phenotype☆

Ampliando el fenotipo del síndrome FOXG1

Dear Editor,

FOXG1 syndrome is an epileptic-dyskinetic encephalopathy initially described as a variant of Rett syndrome (OMIM #613454). In most cases, this neurodevelopmental disorder is caused by mutations in the *MECP2* gene; it exclusively affects women. Rett syndrome is characterised by developmental regression between 6 and 18 months of age, stereotypic hand movements, microcephaly, seizures, and intellectual disability. The condition presents a broad phenotypic spectrum and genetic heterogeneity: it has been associated with microdeletions and translocations in various genes, including *CDKL5* (also known as *STK9*), *NTNG1*, and more recently *FOXG1*. *FOXG1*, located on chromosome 14q12, plays a significant role in brain development,[1] regulating early embryonic development of the telencephalon in the fetus; it is also expressed in adulthood.[2] We present the case of a patient with a heterozygous mutation in *FOXG1*, which supports the notion that FOXG1 syndrome is a distinct entity rather than a variant of Rett syndrome.

Our patient, a 3-year-old boy from Colombia, was born to consanguineous parents following an uneventful second pregnancy. He was born in week 37 of pregnancy by caesarean delivery, with a birth weight of 2680 g (10th-50th percentile), length of 47 cm (10th-50th percentile), and a head circumference of 35.5 cm (50th-90th percentile). No perinatal complications were recorded; an evaluation performed at 3 months by the paediatric neurology department revealed a bulging anterior fontanelle and slightly increased muscle tone. An axial CT scan of the head with 3D reconstruction revealed open opercula, enlarged zygomatic bones, no craniosynostosis, microcephaly, flat occiput, and head circumference 2 standard deviations (SD) below the mean. The patient was further assessed by the paediatric ophthalmology and clinical genetics departments due to psychomotor retardation and gastro-oesophageal reflux disease. The ophthalmological examination revealed partial binocular fixation, repetitive head movements, and abnormal visual behaviour for his age, associated with global developmental delay.

At 3 years of age, the patient had a weight of 8.7 kg (−2.25 SD), a height of 82 cm (−0.53 SD), a low weight-to-height ratio (−2.75 SD), a BMI of 12.9 kg/m^2 (−2.91 SD), a head circumference of 40 cm (−2 SD), microcephaly, flat occiput, prominent metopic ridge, prominent forehead, convergent strabismus, low nasal bridge, smooth philtrum, anteverted ears, tongue protrusion, and shawl scrotum. A metabolic study revealed no alterations and tests for mucopolysaccharidosis yielded negative results. G-banding revealed a normal chromosome complement (46,XY) and findings from microarray-based comparative genomic hybridisation were normal with regions of homozygosity. Exome sequencing of the patient and his parents was performed with the Illumina TruSight One sequencing panel kit and the Next Seq 500 system. An analysis of the genes related to our patient's clinical diagnosis revealed a heterozygous mutation in *FOXG1* (NM_005249.4): c.1107:1108insG, p.Glu371GlyfsTer84, in which the insertion of a guanine results in a premature stop codon, causing a truncated protein. This variant has not previously been reported. However, the literature describes mutations affecting the transcription of the same amino acid (c.460dupG, p.e154GfsX301), which are reported to be pathogenic as they result in the loss of 3 protein-binding domains.[3] Presence of the candidate variant was confirmed with Sanger sequencing; DNA sequencing of the parents revealed that this was a de novo mutation. In summary, our patient displayed poor growth, postnatal microcephaly, poor visual contact and social interaction, convergent strabismus, tongue protrusion, gastro-oesophageal reflux disease, flat feet, neonatal hypotonia, neonatal irritability, delayed motor development, apraxia, stereotypic movement, lack of language, poor sleep pattern, EEG alterations, normal MRI findings, and a de novo mutation. These findings show a genotype-phenotype correlation with atypical Rett syndrome secondary to *FOXG1* mutations.

FOXG1 mutations are extremely rare, presenting in 1%-2% of patients with suspected autism spectrum disorders and 1.5% of female patients with severe intellectual disability and microcephaly.[4] *FOXG1* acts as a transcriptional

☆ Please cite this article as: Candelo E, Caicedo G, Pachajoa H. Ampliando el fenotipo del síndrome FOXG1. Neurología. 2020;35:207—211.

Table 1 Characteristics of the cases of FOXG1 syndrome reported in the literature.

Characteristics	Fryssira et al. (2016)	Cellini et al. (2015)	Mencarelli et al. (2010)	Philippe et al. (2010)	Kortüm et al. (2010)	Ariani et al. (2008)	Papa et al. (2008)	Bisgaard et al. (2006)	Shoichet et al. (2005)	Kamnasaran et al. (2001)	Total	%
Female patients	1/1	6/8	4/4	2/2	5/11	2/2	1/1	1/1	1/1	2/4	25/35	71
Age, years (range)	0.6	(0-10.7)	(3-11.7)	(8-22)	(2-31)	(7-22)	7	14	7	(3-7)	(3-13.7)*	
Uneventful perinatal period[b]	ND	ND	4/4	2/2	11/11	2/2	0/1	1/1	1/1	4/4	25/26	96
Onset within the first months of life[a]	1/1	5/8	4/4	2/2	11/11	2/2	1/1	1/1	1/1	4/4	32/35	91
Developmental regression	0/1	ND	4/4	0/2	2/11	0/2	1/1	ND	0/1	0/4	7/26	27
Lack of language acquisition[a]	1/1	8/8	4/4	1/2	11/11	2/2	ND	ND	0/1	ND	27/35	77
Able to sit up	0/1	ND	1/4	1/2	3/10	1/2	ND	ND	0/1	1/1	7/21	33
Normal development of hand skills	0/1	ND	0/4	1/2	8/11	0/2	1/1	ND	0/1	ND	10/22	45
Able to walk[b]	0/1	2/8	0/4	1/2	1/11	0/2	0/1	ND	0/1	ND	4/30	13
Typical phases of the disease (regression, stabilisation, decline)	0/1	0/8	0/4	0/2	0/11	0/2	0/1	ND	0/1	0/4	0/30	0
Respiratory disorders	ND	ND	0/4	0/2	ND	2/2	ND	ND	ND	ND	2/8	25
Vasomotor dysfunction	ND	ND	1/4	0/2	ND	2/2	1/1	ND	ND	1/1	5/10	50
Irritability[a]	1/1	6/8	4/4	1/2	5/10	2/2	ND	ND	1/1	ND	20/28	71
Hypotonia[b]	0/1	6/8	4/4	1/2	10/10	ND	1/1	ND	0/1	4/4	26/31	84
Postnatal microcephaly[a]	1/1	7/8	3/4	1/2	6/8	2/2	ND	1/1	1/1	2/4	24/31	77
Facial dysmorphism[b]	1/1	8/8	3/4	1/2	2/3	2/2	1/1	1/1	1/1	3/4	23/27	85
Strabismus[b]	1/1	1/8	3/4	1/2	ND	2/2	ND	ND	0/1	1/1	9/19	47
Hypermetropia	ND	ND	1/4	0/2	ND	ND	1/1	1/1	0/1	ND	3/9	33
Bruxism[a]	ND	ND	3/4	1/2	5/8	2/2	1/1	ND	ND	ND	12/17	71
Sialorrhoea	ND	ND	2/4	1/2	ND	2/2	ND	ND	0/1	ND	5/9	56
Constipation[a]	ND	ND	3/4	ND	ND	2/2	ND	ND	0/1	ND	5/7	71
Gastro-oesophageal reflux disease[a]	1/1	ND	1/4	ND	9/10	0/2	1/1	ND	0/1	2/4	14/23	61
Scoliosis[a]	ND	ND	1/4	0/2	ND	1/2	1/1	ND	ND	ND	3/9	33
Genu valgum	ND	ND	0/4	0/2	ND	1/2	ND	ND	0/1	ND	1/9	11
Flat feet	ND	ND	1/4	0/2	ND	ND	ND	ND	0/1	ND	1/7	14

Table 1 (*Continued*)

Characteristics	Fryssira et al. (2016)	Cellini et al. (2015)	Mencarelli et al. (2010)	Philippe et al. (2010)	Kortüm et al. (2010)	Ariani et al. (2008)	Papa et al. (2008)	Bisgaard et al. (2006)	Shoichet et al. (2005)	Kamnasaran et al. (2001)	Total	%
Talipes equinovarus	ND	ND	ND	2/2	ND	ND	ND	ND	ND	ND	2/2	100
Kyphosis	ND	ND	2/4	ND	ND	1/2	ND	ND	0/1	ND	3/7	43
Severe developmental delay[a]	1/1	8/8	4/4	1/2	11/11	2/2	1/1	1/1	1/1	3/3	33/34	97
Cognitive deficits[a]	ND	8/8	4/4	2/2	11/11	2/2	1/1	ND	1/1	ND	29/29	100
Seizures[a]	1/1	8/8	2/4	1/2	8/10	2/2	1/1	1/1	1/1	0/2	25/30	83
Dystonia[b]	1/1	8/8	1/4	1/2	8/10	2/2	ND	ND	0/1	ND	21/26	81
Autistic behaviour[a]	ND	4/8	1/4	2/2	11/11	2/2	1/1	ND	0/1	3/3	24/32	75
Stereotypies[a]	1/1	7/8	3/4	2/2	8/11	2/2	1/1	ND	0/1	ND	24/30	80
Tongue protrusion	ND	ND	2/4	ND	ND	2/2	ND	ND	0/1	ND	4/7	57
Poor sleep pattern[a]	1/1	6/8	2/4	1/2	8/11	2/2	ND	ND	ND	2/2	22/30	73
EEG alterations[b]	1/1	8/8	ND	1/2	8/10	2/2	1/1	1/1	0/1	ND	22/26	85
Reduced number of cortical gyri[b]	0/1	3/8	0/4	0/2	11/11	0/2	0/1	0/1	0/1	0/3	14/34	41
Pachygyria[a]	0/1	ND	0/3	0/2	3/11	0/2	0/1	0/1	0/1	1/3	4/25	16
Corpus callosum hypoplasia[a]	0/1	6/8	2/4	1/2	9/11	2/2	0/1	0/1	0/1	0/3	20/34	59
Corpus callosum agenesis	0/1	ND	0/4	0/2	1/11	0/2	0/1	0/1	1/1	3/3	5/26	19
Ventriculomegaly	0/1	ND	1/4	1/2	5/6	0/2	0/1	0/1	1/1	0/3	8/21	38
Reduced frontal white matter volume[a]	0/1	ND	1/4	1/2	8/11	0/2	0/1	0/1	0/1	1/3	11/26	42
Delayed myelination	0/1	5/8	1/4	0/2	0/11	0/2	0/1	0/1	1/1	1/3	8/34	24
De novo mutation[b]	Del. (*FOXG1-NOVA1*)	8/8	2/2	2/2	11/11	2/2	1/1 deletion	1/1 translo-cation	1/1 translo-cation	ND	20/29 deletion	69

[a] Characteristics described by Kortüm et al.
[b] Characteristics frequently reported in the literature.
* Interquartile range.
Del.: deletion; ND: no data.

Table 2 Major and minor diagnostic criteria and imaging characteristics of FOXG1 syndrome.

Major diagnostic criteria
1. De novo mutation (translocation or deletion)
2. Cognitive deficits
3. Uneventful perinatal period, onset within the first months of life
4. Postnatal microcephaly
5. Hypotonia
6. Severe developmental delay, lack of language acquisition
7. EEG alterations
Minor diagnostic criteria
Irritability, facial dysmorphism (prominent forehead, anteverted ears, hypertelorism), strabismus, bruxism, constipation, gastro-oesophageal reflux disease, seizures, dystonia, poor sleep pattern, stereotypies, autistic behaviour
Imaging criteria
Pachygyria, reduced number of cortical gyri, corpus callosum hypoplasia, reduced frontal white matter volume

repressor. It is highly expressed in the ventricular side of the neuroepithelium in the telencephalon and in visual structures and testicular tissue,[5] promoting the proliferation of progenitor cells and early suppression of neurogenesis and neuronal differentiation.[6] This is achieved through the recruitment of transcriptional repressor proteins Groucho and JARID1B, which participate in the methylation of histone 3 at lysine 4 residues, resulting in chromatin silencing.[7] Molecular analyses have shown that *FOXG1* shares metabolic pathways with *MECP2* during neuronal development; furthermore, the 2 genes show similar expression profiles in postnatal cortical and subnuclear tissue.[8]

FOXG1 is the candidate gene for monogenic 14q12 microdeletion syndrome. Our patient had psychomotor delay, in spite of which he was able to sit up and walk. This illustrates the haploinsufficiency of *FOXG1*, which causes less severe manifestations; a large proportion of the patients described in the literature reach such developmental milestones as walking (3 out of 8 patients). Some studies conclude that heterozygous *FOXG1* variants do not necessarily cause brain malformations,[9] as exemplified by our case.

Atypical Rett syndrome has been linked to mutations in several genes, including *CDKL5* (also known as *STK9*), *NTNG1*, and *FOXG1*. Clinical manifestations in *FOXG1* mutation carriers, however, are considerably different from those observed in patients with Rett syndrome. This explains why some authors suggest that FOXG1 syndrome is clinically and genotypically distinct from Rett syndrome and presents such distinctive clinical characteristics as hyperkinetic dyskinesia.[10] We analysed the published cases of 35 patients with de novo point mutations, deletions, and translocations in *FOXG1*, with clinical phenotypes depending on a wide genotypic variability. FOXG1 syndrome affects both sexes (69% females). A large proportion of these patients do not show developmental regression or the typical stages of Rett syndrome; on the contrary, the associated alterations appear in the neonatal period. Table 1 summarises the characteristics of FOXG1 syndrome described by Kortüm et al.[10]; we have added several other characteristics appearing in over 75% of the published cases, expanding and better defining the phenotype of the syndrome.

FOXG1 syndrome is caused by mutations; as is the case with such chromosomal rearrangements as deletions or translocations in 14q12-q13, the condition causes epileptic-dyskinetic encephalopathy, with a well-defined phenotype.[10] FOXG1 syndrome was first described as a variant of Rett syndrome, as both conditions share clinical characteristics; however, they also present significant differences. Table 2 lists the major and minor clinical features of the syndrome, according to the frequency reported in the literature, and the most frequent imaging findings.

Funding

This study was funded by Icesi University.

References

1. Roth M, Bonev B, Jennefer L, Lea R, Panagiotaki N, Houart C, et al. FoxG1 and TLE2 act cooperatively to regulate ventral telencephalon formation. Development. 2010;137:1553—62.
2. Eagleson KL, Schlueter LJ, Ketchum McF, Ahrens ET, Mills PH, Does MD, et al. Disruption of Foxg1 expression by knock-in of cre recombinase: effects on the development of the mouse telencephalon. Neuroscience. 2007;148:385—99.
3. Kortüm F, Das S, Flindt M, Morris-Rosendahl DJ, Stefanova I, Goldstein A, et al. The core FOXG1 syndrome expression by knock-in of cre recombinase: effects on the development of the mouse telencephalon. Neuroscience. 2007;148:385—99.
4. Bahi-Busson N, Nectoux J, Girard B, van Esch H, de Ravel T, Boddaert N, et al. Revisiting the phenotype associated with FOXG1 mutations: two novel cases of congeniyal Rett variant. Neurogenetics. 2010;11:241—9.
5. Bourguignon C, Li J, Papalopulu N. XBF-1, a winged helix transcription factor with dual activity, has a role in positioning neurogenesis in Xenopus competent ectoderm. Development. 1998;125:4889e900.
6. Xuan S, Baptista CA, Balas G, Tao W, Soares VC, Lai E. Winged helix transcription factor BF-1 is essential for the development of the cerebral hemispheres. Neuron. 1995;14:1141—52.
7. Ariani F, Hayek G, Rondinella D, Artuso R, Mencarelli MA, Spanhol-Rosseto A, et al. FOXG1 is responsible for the congenital variant of Rett syndrome. Am J Hum Genet. 2008;83:89—93.
8. Brunetti-Pierri N, Paciorkowski AR, Ciccone R, Mina ED, Bonaglia MC, Borgatti R, et al. Duplications of FOXG1 in 14q12 are associated with developmental epilepsy, mental retardation, and severe speech impairment. Eur J Hum Genet. 2011;19:102—7.
9. Papa FT, Mencarelli MA, Caselli R, Katzaki E, Sampieri K, Meloni I, et al. A 3 Mb deletion in 14q12 causes severe mental retardation, mild facial dysmorphisms and Rett-like features. Am J Med Genet A. 2008;146:1994—8.
10. Kortüm F, Das S, Flindt M, Morris-Rosendahl DJ, Stefanova I, Goldstein A, et al. The core FOXG1 syndrome phenotype consist of postnatal microcephaly, severe mental retardation, absent

language, dyskinesia, and corpus callosum hypogenesis. J Med Genet. 2011;48:396—406.

E. Candelo[a], G. Caicedo[a], H. Pachajoa[a,b,*]
[a] *Centro de Investigaciones en Anomalías Congénitas y enfermedades Raras, Universidad ICESI, Cali, Colombia*
[b] *Fundación Clínica Valle de Lili, Cali, Colombia*

*Corresponding author.
E-mail address: hmpachajoa@icesi.edu.co (H. Pachajoa).

https://doi.org/10.1016/j.nrleng.2017.09.012
2173-5808/

Subacute central pontine myelinolysis secondary to hyperglycaemia☆

Mielinólisis central pontina de curso subagudo secundario a hiperglucemias

Dear Editor:

Osmotic demyelination syndrome is a rare, severe neurological disease that includes extrapontine and central pontine myelinolysis (CPM), with the latter being the most frequent form. The condition was first described in 1959 by Adams et al.[1] It is typically observed in alcoholic patients and patients with liver transplant or in a hyperosmolar state (particularly after rapid correction of chronic hyponatraemia). However, the syndrome has been also described in situations of severe hyperosmolar state not associated with hyponatraemia, including diabetes mellitus, severe hypophosphataemia, hypokalaemia, kidney failure, haemodialysis, hyperemesis gravidarum, anorexia nervosa, Wilson disease, severe burns, systemic lupus erythematosus, acute intermittent porphyria, cytomegalovirus hepatitis, Epstein-Barr virus—associated haemophagocytic lymphohistiocytosis, anaphylactic shock, and heatstroke.[2,3] Apparently, any sudden alteration in the hyperosmolar state may trigger onset of this syndrome.

We present the case of a 52-year-old man with personal history of type 2 diabetes mellitus with associated microvascular complications; poor metabolic control (last recorded value of glycosylated haemoglobin of 11.7% 4 months earlier); dyslipidaemia; history of intravenous drug use (with no other substance abuse); stage C3 HIV infection with good immunovirological condition; and decompensated hepatic cirrhosis due to HCV genotype 3 infection, which resolved with sofosbuvir and daclatasvir but presented persistent severe complications in recent months (episodes of hepatic encephalopathy, bleeding gastric varices, and fluid retention) as a consequence of a very advanced cirrhosis. The patient was awaiting assessment to be placed on the waiting list for liver transplantation.

The patient also presented a 2-month history of dysarthria, dysphagia, and gait instability. The physical examination revealed moderate dysarthria, limited upgaze, and marked truncal ataxia. A laboratory analysis performed at admission showed glucose concentration of 406 mg/dL, creatinine of 1.37 mg/dL, Na 133 mmol/L, K 4.62 mmol/L, and no other relevant findings. A brain computed tomography study revealed no abnormalities; the cerebrospinal fluid analysis performed within 24 hours of admission (biochemical [including oligoclonal bands], cytological, and microbiological studies [polymerase chain reaction] testing for herpes viruses 1 and 2, *Listeria* antigens, meningococcus, pneumococcus, *Haemophilus*, enterovirus, Epstein-Barr virus, varicella zoster virus, cytomegalovirus, fungal infection, HIV viral load, and mycobacteria) yielded no pathological results. A brain magnetic resonance imaging (MRI) study (Fig. 1) performed at 48 hours of admission showed a hyperintense lesion to the pons on proton-density/T2-weighted and FLAIR sequences, with discrete diffusion restriction; all these findings are compatible with CPM.

Considering the patient's history, we concluded that he had presented resolved hyponatraemia that was not detected in previous analyses, with only high glycaemic values (around 500-600 mg/dL) persisting; this would cause a hyperosmolar state, triggering CPM. The remaining analytical parameters were normal (biochemistry, ions, autoimmunity, tumour markers, antineuronal antibodies, and toxicology). During hospitalisation, glycaemic levels were well controlled, with progressive neurological improvement; at discharge, the patient presented mild dysarthria only. A 5-month follow-up examination showed complete resolution of neurological symptoms, and a brain MRI scan displayed clear lesion improvement (Fig. 2).

The pathophysiological mechanisms of CPM are not yet well established, but they are believed to be a consequence of blood—brain barrier disruption secondary to osmotic stress, leading to demyelination and oligodendrocyte apoptosis.[4]

Ashrafian and Davey[5] have suggested that aetiology is multifactorial and that the syndrome is more likely to present in patients with conditions predisposing to deficiencies in the supply of energy to neurons and glial cells. They also observed that patients with slow correction of hyponatraemia may develop CPM if electrolytic alterations occur during a state of energy deprivation, such as chronic alcoholism or liver disease. These authors report that alcoholic and cirrhotic patients, as well as patients with hypoglycaemia due to other causes, may lack a plentiful supply of glucose or glycogen to glial cells, which is necessary to main-

☆ Please cite this article as: Corps Fernández D, Terrero Carpio R, Escolar Escamilla E, Pinel González A. Mielinólisis central pontina de curso subagudo secundario a hiperglucemias. Neurología. 2020. https://doi.org/10.1016/j.nrl.2017.09.009