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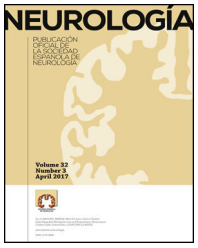

LETTERS TO THE EDITOR

A new case of Pitt-Hopkins-like syndrome 2?☆

¿Un nuevo caso de síndrome de Pitt-Hopkins *like* 2?

Dear Editor:

Neurexins are a small family of cell adhesion proteins which participate in synapsis by binding to the post-synaptic ligand neuroligin and forming calcium-dependent trans-synaptic complexes in the central nervous system.[1—3] Three neurexin genes have been identified in the human genome: *NRXN1*, *NRXN2*, and *NRXN3*. The *NRXN1* gene, located at 2p16.3, is 1.1 Mb long and includes 24 exons.[4]

We present the case of a paediatric patient from south-western Colombia. He was the first child of non-consanguineous parents, and was born after a full-term pregnancy with medical care during delivery. The first examination of the neonate revealed right cryptorchidism and heart murmur; an echocardiography revealed peripheral pulmonary stenosis, tricuspid insufficiency, and left ventricular hypertrophy.

At 4 years of age, the patient was referred to a paediatric genetics clinic; physical examination revealed dolichocephaly, prominent forehead, coarse hair and dry skin, bitemporal hair thinning, bulbous nose, fingers with bilateral clinodactyly, autistic behaviour (including self-harm), and cognitive deficits.

The patient underwent several studies including G-banding (46, XY with no numerical or structural alterations), computed tomography, and magnetic resonance imaging, revealing posterior ventricular asymmetry with right ventricular dilatation, anatomical changes to the ventricular floor, and mega cisterna magna.

Metabolic screening, array comparative genomic hybridisation, and a molecular panel for RASopathies yielded negative results. Neuropsychological evaluation revealed severe autism with a score of 94 on an autism spectrum scale (minimum 24/maximum 96). We requested a 101-gene molecular panel for autism, including *NRXN1*, which showed 2 mutations in heterozygosis. In the first mutation, cytosine was replaced by thymine at position 1405 (c.1405C>T), presumably causing the replacement of proline by serine at position 469 (p.Pro469Ser) [rs7850316]; in the second mutation, adenine was replaced by guanine at position 4053 (c.4053A>G), resulting in the replacement of alanine by alanine at the 1351 position (p.Ala1351Ala) [rs7997075]. The parents were assessed for both mutations; the father was found to carry the c.1405C>T variant (p.Pro469Ser) [rs7850316] in heterozygosis and the mother was a carrier of the c.4053A>G variant (p.Ala1351Ala) [rs7997075] in heterozygosis.

The literature includes reports of 3 cases of patients with biallelic mutations of the *NRXN1* gene with a similar phenotype, who were finally diagnosed with an entity called Pitt-Hopkins-like syndrome 2.[5,6] We believe that our patient may be the fourth case of Pitt-Hopkins-like syndrome 2, but the first to present a heterozygous mutation of the *NRXN1* gene not associated with deletions in the 2p16.3 region.

The c.1405C>T variant (rs78540316) is classified in the Clinical Variant database as a change of uncertain clinical significance. An in silico analysis provided contradictory results, with the SIFT software predicting that this is probably a tolerated change, whereas the PolyPhen-2 software predicted that it was probably pathological. However, a comparative analysis of the phenotypes of our case and those reported by Zweier et al.[6] and Harrison et al.[5] (Table 1) shows a significant overlap of signs and symptoms, the exceptions being the posterior ventricular asymmetry with right ventricular dilatation, the anatomical changes to the ventricular floor, and the mega cisterna magna.[5—7] These findings may be a new addition to the phenotypic spectrum of Pitt-Hopkins-like syndrome 2, and are probably due to the specific mutations present in our patient.

We should mention that the previously reported cases of Pitt-Hopkins-like syndrome 2 present a deletion-type mutation in homozygosis affecting *NRXN1*,[5—7] suggesting an autosomal recessive inheritance pattern; however, our case presents a nucleotide substitution in heterozygosis, also present in the father. Therefore, in this case, the mutation (c.1405C>T) is considered to follow an autosomal dominant inheritance pattern with incomplete penetrance, or to be caused by the co-occurrence of mutations c.1405C>T and c.4053A>G, in which case our patient would be a compound heterozygote for *NRXN*, which would justify the healthy phenotypes of the parents.

The significant phenotypic similarities with the previously reported patients, in association with the presence of a mutation in the *NRXN1* gene, lead us to believe that our patient has the same condition. This supports the idea that mutations in the *NRXN1* gene cause a phenotype consisting in autism and cognitive deficit similar to that observed in Pitt-Hopkins syndrome.

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Table 1 Comparison of the phenotypes of patients previously reported with Pitt-Hopkins-like syndrome 2 and the present case.

Characteristics	Zweier et al.[6]	Harrison et al.[5]	Harrison et al.,[5] sister of proband	Our patient
Age	18 years	16 years	11 years	7 years
Sex	Female	Female	Female	Male
Parents	Healthy	Healthy	Healthy	Healthy
Height	P50-P75	$P < 0.4$	P25	P90.3
Weight	P50-P75	$P < 0.4$	P25	P34.5
Head circumference	P25	P0.4-P9	P9	P60.8
Intellectual disability	Severe	Severe	Severe	Severe
Age of walking onset	2 years	5 years	None	2 years
Speaking	None	20-25 words	None	None (total or functional mutism with non-linguistic verbalisations)
Age of seizure onset	None	At 6 months	At 4 months	None
MRI findings	Normal	Normal	Normal	Posterior ventricular asymmetry with right ventricular dilatation, mega cisterna magna, and anatomical changes to the ventricular floor and cerebellar lobes
Hyperventilation	Yes	Yes	Breath holding	Yes
Stereotypies	Yes	Yes	Yes	Yes
Autistic behaviour	Yes	Not reported	Not reported	Yes
Developmental regression	Normal during the first years	Normal during the first months (up to seizure onset)	Slow development with no regression	Normal during the first year
Constipation	Yes	Yes	Yes	Yes
Abnormal sleep-wake cycles	Yes	Yes	Yes	No
Other	—	Self-harm	—	Self-harm
	—	Pulmonary stenosis	Pulmonary stenosis	Left ventricular hypertrophy. Pulmonary stenosis and tricuspid insufficiency
	—	Hypotonia	Hypotonia	Hypotonia
	Strabismus	—	—	Strabismus
	Hypermotor behaviour	—	—	Hypermotor behaviour
	—	Gastro-oesophageal reflux	Gastro-oesophageal reflux	Gastro-oesophageal reflux
	—	—	—	Constipation
	—	Early puberty (9 years)	Early puberty (6 years)	—
	—	Scoliosis	Scoliosis	—
	Wide mouth and protruding tongue	—	—	Protruding tongue
	Sialorrhoea	—	—	Sialorrhoea
	Decreased deep tendon reflexes: UL: decreased LL: normal	—	—	Decreased deep tendon reflexes: UL: decreased LL: decreased
	—	Bruxism	—	—

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Ischaemic stroke as the predecessor event of an episode of thrombotic thrombocytopenic purpura☆,☆☆

Ictus isquémico como evento predecesor de brote de púrpura trombótica trombocitopénica

Dear Editor,

Thrombotic thrombocytopaenic purpura (TTP) is an infrequent haematological disease characterised by thrombocytopaenia and haemolytic anaemia. Neurological complications are relatively frequent during the development of the disease, and manifest after onset of clinical and analytical haematological symptoms.[1] We present the case of a woman with TTP whose neurological complications (recurrent ischaemic strokes) preceded a new episode of TTP activity.

Our patient is a 36-year-old woman diagnosed with TTP in 1998 after presenting multiple haematomas in the context of microangiopathic haemolytic anaemia and thrombocytopaenia. Due to acute-onset dysarthria and weakness in the right limbs, she was admitted to the neurology department with suspected acute ischaemic stroke. The neuroimaging study revealed focal hypoperfusion in the left parietal region, with no filling of the distal M2 segment of the left middle cerebral artery. A follow-up MRI scan revealed multiple acute punctiform ischaemic lesions in the left temporo-parietal region (Fig. 1). The aetiological study revealed no blood alterations (Table 1) or paroxysmal disorders of heart rate (normal Holter ECG and telemetry findings), and a transoesophageal echocardiography ruled out the presence of cardioembolic sources. We diagnosed ischaemic stroke of undetermined cause and recommended antiplatelet treatment (acetylsalicylic acid) at discharge. Fifteen days after the first admission, the patient presented dysaesthesia in the face and right hand. In this instance, neuroimaging studies (CT and MRI) did not reveal acute alterations. The laboratory analysis only revealed the presence of isolated schistocytes (low schistocyte levels might be considered normal in healthy individuals, not suggesting disease), with no other pathological findings (Table 1). Seven days after the second event, she presented symptoms of asthenia with haematomas in the lower limbs. A new analysis revealed thrombocytopaenia and haemolytic anaemia. Matrix metalloproteinase ADAMTS13 activity was 0% (normal activity, 6%-100%), and the anti-ADAMTS13 IgG antibody titre was 80 IU/mL (Table 1). After diagnosis of a TTP episode, treatment was started with plasma exchange, corticosteroids, and rituximab, with the patient showing a progressive improvement in both clinical and analytical parameters.

TTP is a rare haematological disease whose neurological manifestations occur during the development of the disease (including stroke and transient ischaemic attacks).[1] We present a patient whose cerebral ischaemic events preceded the haematological changes typical of active TTP, which is extremely infrequent.[2—6] Thrombotic complications of TTP are caused by an immune-mediated phenomenon which causes the inactivation of the ADAMTS13 metalloprotease enzyme, responsible for degrading high-molecular-weight Von Willenbrand factor multimers. Accumulation of those

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☆☆ This study was submitted in poster format for presentation at the 68th Annual Meeting of the Spanish Society of Neurology and at the 5th Stroke Competition of the Spanish Society of Neurology.