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Letter to the Editor

Expanding the phenotype of phosphomannomutase-2 gene congenital disorder of glycosylation: Cervical dystonia

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Jaeken syndrome

Dear Editor

Phosphomannomutase-2 deficiency-congenital disorder of glycosylation (PMM2-CDG), congenital disorder of glycosylation type-Ia or Jaeken syndrome (MIM #601785) is an autosomal recessive inherited condition of abnormal glycosylation of N-linked oligosaccharides [1]. Disease course is variable, ranging from infantile forms with multisystem involvement and a childhood-adult ataxia-intellectual disability type with neurologic stable form [1,2]. The phenotypic spectrum includes morphological abnormalities, ataxia, developmental delay, strabismus, retinopathy, seizures, stroke-like episodes, peripheral neuropathy, hypergonadotropic hypogonadism and thrombotic events [2,3]. Brain imaging displays cerebellar and brainstem atrophy. We describe two sisters with PMM2-CDG that present with cervical dystonia that to our knowledge has not been previously reported.

Thirty-three and 30-year-old sisters born to non-consanguineous healthy parents of Spanish-Italian ancestry were studied. There was no other remarkable family history (Fig. 1).

Both patients were the product of an uneventful pregnancy with no delivery complications. At 4 months of age, patient III:3 showed a developmental delay. At three years-old, unsteady gait was detected. Strabismus was surgically treated. At the age of five years, action limb incoordination and tremor were recognized and from ten to twenty-one years of age, axial and appendicular ataxia increased. Since then, she began to experience progressive abnormal twisted and sustained posture of the neck with slight jerks. Currently, she is in part-time employment as assistant in a bakery and performs all activities of daily living unaided. On physical examination, she presented slight dysarthria, moderate intellectual disability, slight strabismus, abnormal subcutaneous fat tissue distribution around the hips and upper thighs, kyphoscoliosis, absent deep tendon reflexes in legs and mild limb and gait ataxia. A mild dystonic posture in both hands with dystonic tremor was also present. Slight head rotation and laterocollis to the right, mild retrocollis and dystonic jerks were present (Supplementary video 1). She obtained partial relief by sensory tricks. She denied previous exposure to neuroleptics or other drugs that can induce dystonia.

Index patient III:4 showed failure to thrive and developmental delay from approximately three months of age and delayed language and unsteady gait were detected at two years-old. Axial and appendicular ataxia increased over the past ten years. On physical examination, she displayed moderate dysarthria and intellectual disability, large ears, nystagmus and mild limb and gait ataxia. A slight cervical anterior shift on the sagittal plane was observed (Supplementary video 1). No hand dystonia was present.

Both patients shared the presence of hypergonadotropic hypogonadism and osteopenia. None had multisystemic affectation, seizures, retinopathy, stroke-like episodes, thromboembolic events or inverted nipples.

Patient III:3 received clonazepam at 0.5 mg daily, which reduced significantly dystonic tremor in both hands. Trihexyphenidyl and levodopa (up to 1000 mg/day) were tried for six months without improvement of dystonia. Onabotulinum toxin A injections were applied to patient III:3 in seven occasions with partial but acceptable alleviation of cervical dystonia. Total Toronto Western Spasmodic Torticollis Rating Scale scores improved from 23 (worst) to 11 (best) points in the last and most effective application. Treatment in patient III:4 was not necessary due to minor affectation.

Liver and renal function, antithrombin III levels, prothrombin time and immunoglobulin-A and G levels were normal in both patients. Brain MRI in patient III:3 revealed marked cerebellar and brainstem atrophy (Fig. 2).

Whole Genome Sequencing (Supplementary material) was performed to the affected sisters and their father, after obtaining written informed consent. Two heterozygous mutations in the PMM2 gene in a compound heterozygous state were detected in both patients: c.422G>A, which results in a (p.Arg141His) missense change and c.722G>C, which results in a (p.Cys241Ser) missense change. Both pathogenic variants were reported as disease causing for PMM2-CDG and were classified as pathogenic according to the American College of Medical Genetics and Genomics. The father carried the c.422G>A (p.Arg141His) mutation. There were no variants of unknown significance shared by the two affected siblings in a matching zygosity for the respective associated disease. Genes known to be associated with dystonia were examined, but there were no variants, which would support another diagnosis or that could explain the presence of dystonia. It was not possible

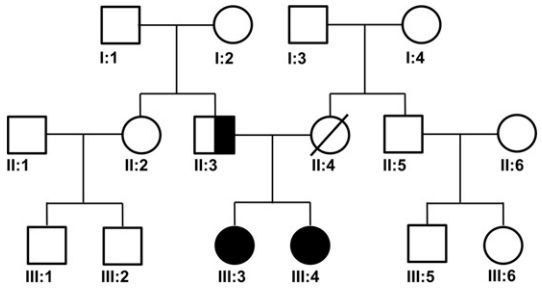

Fig. 1. Pedigree of family exhibiting two variants in a compound heterozygous state in the PMM2 gene. Affected individuals are indicated in black.

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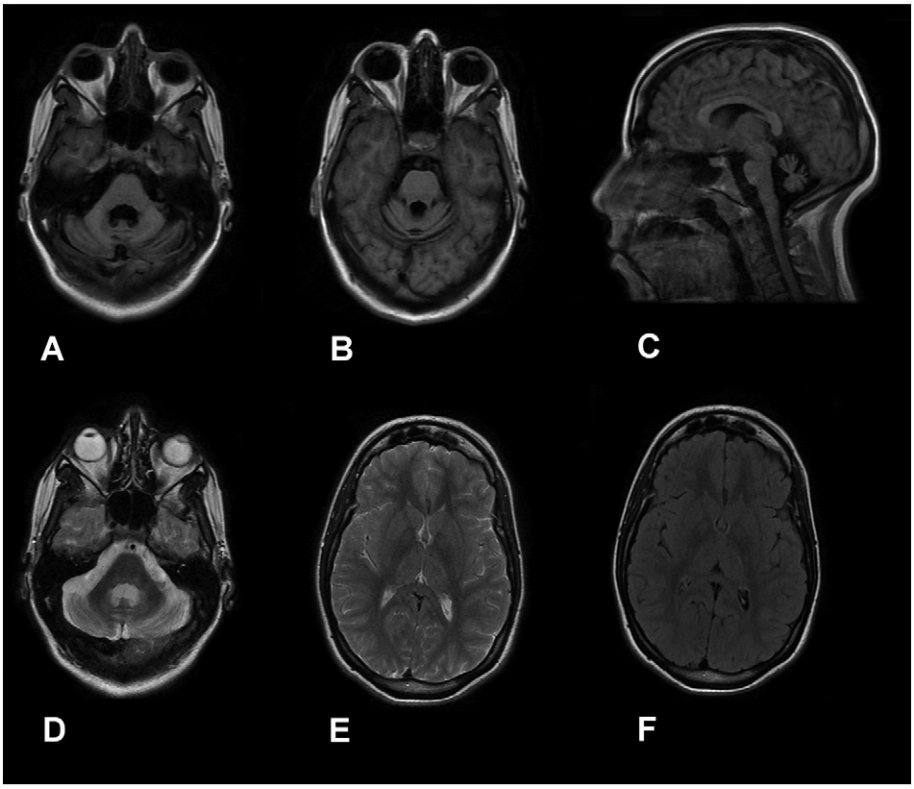

Fig. 2. Brain MRI in patient III:3. Note the marked cerebellar and brainstem atrophy.

to analyze isoelectric focusing of serum transferrin or PMM2 enzyme activity, although it would not have changed patient's diagnosis.

The presence of cervical dystonia expands the clinical spectrum of PMM2-CDG. The only case that to our knowledge reported any type of dystonia was a child with hand dystonic movements [4]. Several genetic disorders may encompass a combination of predominant dystonia and ataxia, such as some spinocerebellar ataxias, ataxia with isolated vitamin E deficiency, some hereditary spastic ataxias, paroxysmal dyskinesias (PxMD-SLC2A1), Leigh syndrome, neurodegeneration with brain iron accumulation, Niemann-Pick disease and Wilson disease. It should be noted that cervical dystonia should be differentiated from skeletal cervical kyphosis because PMM2-CDG patients can have severe spine and thoracic deformities. Postural neck malposition secondary to skeletal deformities may underestimate the possible presence of cervical dystonia in other patients with this condition.

The p.Arg141His mutation present in both patients is also found in the compound heterozygous state in approximately 40% of patients [5]. Mild phenotypes are usually due to the p.Cys241Ser variant that is also present in our patients [2,5].

Patients combining ataxia and dystonia are relatively rare and can cause substantial diagnostic uncertainty. Our cases illustrate the phenotypic variability of PMM2-CDG by adding cervical dystonia to the list of neurological features associated to this condition.

Ethics

Patients signed written informed consent.

Conflicts of interest

None.

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Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2017.04.037.

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