HOMER-3 Antibodies Were Not Detected in Two German Cohorts of Patients with Multiple System Atrophy

Multiple system atrophy (MSA) is a neurodegenerative disease with progressive disability and reduced life expectancy.[1] Patients suffer from predominant cerebellar or parkinsonian symptoms combined with autonomic failure. In recent years, an increasing number of autoantibodies were detected that can evoke syndromes mimicking neurodegenerative diseases.[2] In this group of newly discovered antibodies, HOMER-3 autoantibodies were reported to mimic an MSA phenotype with cerebellar ataxia, dysautonomia, rapid eye movement (REM) sleep behavior disorder, and a hot cross bun sign on structural MRI in an Asian population.[3] In a cohort of 750 Asian patients suspected for autoimmune cerebellar ataxia, six patients had HOMER-3 antibodies in the serum, and two of these six also in cerebrospinal fluid (CSF).[3] One-third (2/6) of these HOMER-3-positive patients presented with clinical and magnetic resonance imaging (MRI) signs compatible with MSA. Interestingly, these patients presented the HOMER-3 antibody only in serum.[3] Because this HOMER-3-antibody related disease is a potentially treatable condition, our current study aimed to identify the prevalence of HOMER-3 autoantibodies in clinically diagnosed MSA patients.

Therefore, patients of European origin from two German biobank cohorts, diagnosed according to the Gilman criteria for clinical diagnosis of possible or probable MSA[4] were analyzed with a research-grade HOMER-3 antibody assay (Euroimmun, Lübeck, Germany).[3,5] In total, 59 patients (25 female) with a mean age of 61.5 ± 8.4 were included in this study. Of these, 33 presented with a cerebellar (MSA-C) and 26 with a parkinsonian phenotype (MSA-P). The mean disease duration was 3.7 ± 2.3 years. In none of these patients we were able to detect HOMER-3 antibodies in serum.

The preexisting data indicate that HOMER-3 antibody associated cerebellar ataxia may be a rare, but potentially treatable differential diagnosis for MSA.[3,5,6] Based on our data, systematic screening of all patients with clinically suspected MSA cannot be generally recommended. The frequency of HOMER-3 positive patients needs to be determined in larger MSA cohorts of diverse ethnicities, and the specific clinical and imaging phenotype of this autoimmune disease needs to be further elaborated to identify specific features, which would encourage HOMER-3 testing in individual patients not to be missed for individualized therapies.[7]

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Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. We obtained approval of the local institutional review boards for this work (MHH: 8666_BO_K_2019; LMU: 18-353). Written informed consent was obtained from every participant.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Isolated Paroxysmal Non-kinesigenic Dystonia Associated with Homozygous *PDHB* Variant in an Indian Family

Although *MR-1/PNKD* variants are the most common cause of inherited paroxysmal non-kinesigenic dyskinesia (PNKD), in a large proportion of PNKD patients, the underlying genetic basis remains unknown.[1] Pyruvate dehydrogenase (PDH) complex deficiency causes phenotypes ranging from fatal infantile lactic acidosis to mental retardation or intermittent ataxia.[2] Brain imaging may reveal cortical atrophy, ventricular dilatation, basal ganglia (BG) abnormalities, and corpus callosum agenesis.[2] PDH deficiency might result from variants in genes encoding discrete subunits of the PDH complex. The majority is caused by *PDHA1* variants, whereas a minority is caused by variants in *PDHB*, *DLAT*, *DLD*, *PDHX*, or *PDP1*. Paroxysmal dyskinesia (PxD) is an infrequent, poorly characterized feature in a few cases of PDH deficiency caused by *PDHA1* or *DLAT* variants.[3,4] Here, we report isolated PNKD in 2 siblings, associated with a novel homozygous pathogenic variant in *PDHB*, the gene coding for the E1β subunit of the PDH complex.

The siblings were born to consanguineous parents of Indian origin (Fig. 1A). The proband (II-1) experienced repeated falls due to episodes of hemi- or bilateral lower-limb predominant dystonia, with onset at age 5 years (Video S1, Segment 1). The episodes typically lasted 1 to 2 hours, were not precipitated by movement, and would occur without warning. Interictal examination was normal. Serum biochemistry, electrolytes, calcium, urine gas chromatography/tandem mass spectrometry for metabolic diseases, and tests for Wilson's disease were unrevealing. Nerve conduction studies and electroencephalograms were normal. Lactate and pyruvate levels in blood and cerebrospinal fluid were normal, as observed previously in individuals with *DLAT* variants.[3] Brain magnetic resonance imaging (MRI) revealed symmetric T2 pallidal hyperintensities on T2 and FLAIR (Fig. 1C, II-1). Levodopa, trihexyphenidyl, clonazepam, and baclofen were unhelpful. Carbamazepine (CBZ) at 300 mg/day led to a 90% to 95% reduction in frequency, severity, and duration of the episodes.

Three years later, his younger brother (II-2) manifested identical episodic hemidystonia mainly affecting one foot or leg (Video S2, Segment 2), with T2 hyperintensities in the dentate nucleus (Fig. 1C, II-2). His attacks also responded near-completely to CBZ (200 mg/day).

Pallidal lesions in patients with isolated paroxysmal dystonia have been described in patients with PDH deficiency (due to variants in *DLAT*[3], *PDHA1*,[4] and *PDHX*) and due to *ECHS1* variants.[5] However, analysis in the proband's WES (Whole Exome Seqencing) (Appendix S1) did not reveal any variants in these genes or other genes causing PxD (Table S1). Instead, we found a homozygous variant in *PDHB*, c.856A>G/p.Thr286Ala (Table S2), absent in databases and predicted damaging by most in silico tools (Table S3).

The phenotypic spectrum observed with biallelic *PDHB* variants is similar to that observed with *PDHA1*[6] but with unclear genotype–phenotype correlations. A review of 82 patients with PDH deficiency included 65 patients with *PDHA1* variants, 9 with *PDHX*, 7 with *PDHB*, and 1 with *DLD*.[7] In these patients, dystonia was reported in those with *PDHA1* and *PDHX* variants but in none with *PDHB* variants.[7] In contrast, mild dystonia without additional clinical characterization was mentioned in 1 patient with *PDHB* variants and other clinical features.[6] Furthermore, other *PDHB* patients showed abnormal BG/dentate MRI lesions.[6,7] To our knowledge, isolated paroxysmal dystonia has not been described in patients with *PDHB* variants.

After the identification of the *PDHB* variant, the siblings were commenced on thiamine and multivitamin supplementation. The younger brother continues to respond to CBZ, without attack recurrence. In contrast, the proband remains asymptomatic at 3-year follow-up after stopping CBZ. These observations might be of therapeutic relevance, given reports of improvement and even complete reversibility[4] in some patients after thiamine. A trial of thiamine supplementation should be considered in cases of isolated PNKD or PED (Paroxysmal Exercise-induced dyskinesia) with bilateral pallidal lesions.

In conclusion, our patients with PNKD as the only and prominent clinical presentation represent a relevant expansion of the phenotype associated with *PDHB*. Our observation suggests that *PDHB* should be included among the genetic causes of isolated PNKD.

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