Variable Age at Onset in *AOPEP*-Associated Dystonia

With great interest, we read the letter of Menden et al[1] reporting their findings on bi-allelic loss-of-function *AOPEP* variants. Following a statement of hesitance to publish their data because of a homozygous stop variant (c.703C > T, p.(Gln235*)) in a reported healthy 35-year-old male, we present a patient carrying the identical homozygous variant with severe symptoms matching *AOPEP*-associated dystonia.

The male patient noticed twitching in his abdominal muscles during weight training at age 29 and developed severe retrocollis 1-year later with intermittent and irregular dystonic tremor leading to dysphagia and neck pain. Within months, he also developed a gait disturbance with circumduction of the right leg and reduced ipsilateral arm swing. The patient was diagnosed with generalized dystonia (Fahn-Marsden dystonia scales, movement: 25/120, disability: 5/30). He experienced relief of the retrocollis by placing his hand lightly on the back of his head (geste antagoniste). Medication with levodopa and trihexyphenidyl showed no benefit, but he responded well to botulinum toxin injections with the cessation of dystonic tremor and dysphagia after 400 units of incobotulinumtoxin into the cervical and shoulder muscles (every 3 months). The consanguineous parents (second-degree cousins of Turkish origin) and the four younger sisters of the patient had no neurological complaints and received no genetic testing.

Laboratory testing, including electrolytes, liver enzymes, thyroid hormones, iron, ferritin, transferrin, copper (serum and urine), ceruloplasmin, cardiolipin, and rheumatological antibodies, provided normal results. Brain magnetic resonance imaging and dopamine transporter single photon emission computed tomography were normal as well.

A next-generation sequencing-based whole-exome analysis revealed the above-mentioned homozygous nonsense variant of the *AOPEP* gene (NM_001193329.3:c.703C > T, NP_001180258.1: p.(Gln235*)). The genes *ANO3*, *ATP1A3*, *GCH1*, *GNAL*, *HPCA*, *PRKRA*, *SGCE*, *SPR*, *TH*, *THAP1*, *TOR1A*, and *VPS13A* had no abnormal findings.

Our patient and the *AOPEP*-associated dystonia patients reported by Zech et al[2] with similar symptoms and progression, support that the detected homozygous *AOPEP* variant is pathogenically relevant. Further evidence is provided by an additional Turkish-born patient (age, 30–39 years) with *AOPEP*-associated dystonia carrying the same homozygous *AOPEP* variant that was recently listed in the genetic variation interpretation database ClinVar (IDs: 2498245, SCV003915775.1).[3]

Because the healthy subject, ethnic background not mentioned, presented by Menden et al[1] carries the same variant and was (still) asymptomatic at age 35, this might reflect either reduced penetrance or increased variability regarding age at disease-onset because of the gene variant. Currently, the highest reported age at onset in *AOPEP*-associated dystonia is 37 years of age.[4] Follow-up with this subject might not only be relevant for counseling the patient and his family, might also provide insight into the variability of age at onset in this rare disorder. Differences regarding age at onset were also observed in two previously reported pairs of siblings in which each pair had the same genetic mutation, but had a different site[2] and age at onset[2,5] (difference at onset of 2 and 5 years, respectively). The variability of age at disease-onset should be considered when counseling patients with AOPEP-associated dystonia, asymptomatic mutation carriers, and their families.

Author Contributions

MM: Conception, organization, execution, writing of the first draft, review and critique. BL: Conception, execution, writing of the first draft, review and critique. AR: Execution, writing of the first draft, review and critique. TK: Execution, review and critique. JIL: Execution, review and critique. CB: Execution, writing of the first draft, review and critique. AS: Conception, review and critique.

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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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An Indirect Proof for Levodopa-Induced Vitamin Deficiency in Parkinson's Disease

We appreciate the negative outcomes on the putative impact of vitamins B_6, B_{12}, and folate on the incidence of Parkinson's disease (PD).[1] It confirms the neuroprotective potential of vitamin B_{12} in the nervous system.[1] These results end a long and still controversial discussion on the putative role of methyl group–donating vitamins on the pathogenesis of PD and related disorders.[2] This debate also resulted from a certain prior neglect of a levodopa (L-dopa) metabolism–induced consumption of methyl groups. They are needed for the conversion of L-dopa to 3-*O*-methyldopa via the enzyme catechol-*O*-methyltransferase (COMT).[3] This is particularly the case when L-dopa is applied with a dopa decarboxylase inhibitor (DDI) only, which shifts L-dopa turnover via COMT primarily. Therefore, concomitant COMT inhibition may be beneficial during long-term L-dopa/DDI application for metabolic reasons. COMT constraint may weaken the clinical consequences of long-term deficiencies in methyl group–donating vitamins. These lower vitamin levels result in impaired DNA methylation and thus gene dysfunction, deterioration in cognition, and neuropathy.[2-4] We emphasize that no long-term clinical investigations exist to confirm this hypothetical conclusion. One possible therapeutic consequence should be mandatory, nutritional supplementation with methyl group–donating vitamins for the periphery.[2,3] Centrally, L-dopa metabolism via COMT is mainly performed in glial cells. A certain methyl group donation capacity also exists centrally, but homocysteine concentration as the main biomarker for the need of methyl groups was found elevated in the cerebrospinal fluid of long-term L-dopa-/DDI-treated patients.[5] Homocysteine increases when the endogenous, abundant amino acid methionine acts as a methyl group donor for COMT-mediated L-dopa degradation. This process demands a methyl group transfer from the donor *S*-adenosylmethionine. Consequently, *S*-adenosylmethionine is converted into the short-living *S*-adenosyl-homocysteine and then to homocysteine.[6] Homocysteine increase serves as a biomarker for an impaired methylation capacity.[3] Therefore, a protective therapy in L-dopa-treated patients involves the development of a novel, not toxic liver, centrally acting COMT inhibitor. This compound should be applied in conjunction with a monoamine oxidase B inhibitor. Additional glial constraint of monoamine oxidase B declines an enhanced dopamine-induced generation of oxidative stress as a consequence of central COMT inhibition, which probably shifts glial dopamine degradation via monoamine oxidase B. Therapeutic alternatives may involve the application of peripheral-acting and blood–brain barrier–trespassing methyl group–donating and free radical scavenging drugs in chronic L-dopa-treated PD patients. Such a compound is neither known nor in development yet. However, such a future therapy will focus on currently ongoing, still negative, and somewhat frustrating clinical research on the prevention or disease modification in PD, that is, in LRRK2- or glucocerebrosidase mutation carriers, away from relative rare genetically determined PD subtypes toward a more general approach with amelioration of a still underestimated epigenetic drug effect.[3] Therefore, in conclusion we suggest that the missing impact of a higher intake of methyl group–donating vitamins on the incidence of PD will hopefully direct research on novel, more clinical-relevant therapies on the modification of progression in the heterogeneous disease entity PD.[1]

Data Availability Statement

Not applicable.

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