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LETTER TO THE EDITOR

WILEY CNS Neuroscience & Therapeutics

Mitochondrial ataxia is genetically and phenotypically heterogeneous

Dear Editor,

With interest, we read the article by Dong et al about the genetic cause of ataxia in 33 Chinese patients.[1] The included patients were investigated by next-generation sequencing (NGS) for a possible genetic cause of the clinical presentation.[1] The study raises a number of comments and concerns.

We do not agree with the initial statement of the introduction that "ataxia is a heterogeneous group of disorders with multiple types…" Ataxia is a sign and found on clinical neurological examination. If the authors mean hereditary ataxias, the wording needs to be adapted. A major group of hereditary ataxias was not mentioned in the statement about the genetic classification of ataxias, and these are the maternally transmitted ataxias /mitochondrial ataxias).[2]

Ataxia may not only be a phenotypic manifestation of myoclonic epilepsy with ragged-red fibers (MERRF), Kearns-Sayre syndrome (KSS), neuropathy, ataxia, retinitis pigmentosa (NARP), or *POLG1*-associated mitochondrial disorders (MIDs), but may also occur in ponto-cerebellar hypoplasia (PCH6), leukoencephalopathy with brainstem and spinal cord involvement (LBSL), X-linked sideroblastic anemia (XLSA), mitochondrial recessive ataxia syndrome (MIRAS), in patients carrying the mutations m.3243A > G and in a number of other specific or nonspecific MIDs.[3] Cerebellar ataxia may be also associated with mutations in genes affecting mitochondrial functions, such as the *L2HGDH*,[4] *PITRM1*,[5] *COA7*,[6] *VPS13D*,[7] *ACO2*,[8] *NADK2*,[9] *VARS2*,[10] *AIFM1*,[11] and *SLC25A46*,[12] to mention just the ones most recently detected.

Ataxia may not only be due to cerebral causes but also due to abnormalities of the spinal cord or the peripheral nerves.[13] Thus, it is conceivable that among the 33 included patients some had a spinal cord lesion or a sensory or sensorimotor neuropathy. Was ataxia among the 33 included patients classified according to the location of the lesion? Another indicator for sensory ataxia in the cohort studied is that 18% had sensory disturbances and 6% had autonomic dysfunction, which is frequently associated with sensory neuropathy. The authors excluded only some causes of acquired and hereditary neuropathy but many more need to be excluded. How many of the 33 included patients presented with sensory or sensorimotor neuropathy? Exclusion of polyneuropathy as the cause of ataxia is particularly important as 18% of the 33 patients had clumsiness of their hands.

A further shortcoming of the report is the lack of a detailed family history. As the study looked for hereditary diseases, it is important to look thoroughly for nonneurological and neurological abnormalities in addition to ataxia in any of the first-degree relatives of the 33 included patients. This is particularly important as the genotype-phenotype correlation may not be strong in each type of genetic defect, particularly in heteroplasmic mtDNA mutations, and as there may be significant phenotypic heterogeneity between first-degree family members. Different phenotypes within a family can be due to the same mutation, why a genetic link between family members can be easily overlooked.

As spinocerebellar ataxias (SCAs) may be due to mutations in more than the 46 genes tested with the panel, it is important that particularly in the 28 patients in whom no genetic cause for ataxia could be detected by genetic screening, SCA is excluded.

Despite clinical manifestations in some of the first-degree relatives of the five patients in whom a genetic cause of ataxia could be detected, only to one of these relatives was a genetic investigation proposed. However, genetic testing of all relatives is important to assess the type of transmission, to determine the degree of phenotypic heterogeneity and to determine whether the variant was inherited or sporadic.

Finally, we do not agree with the statement that there is no gold standard for assessing the pathogenicity of a mutation.[1] At least for tRNA variants, the pathogenicity can be easily assessed by application of the modified Yarham score.[14] The strength of the genotype-phenotype correlation can be assessed by application of the Smith score.[14]

Overall, this interesting study could be more meaningful by taking a thorough family history from each of the participants, by exclusion of sensory ataxia, by genetic workup in all first-degree relatives, and by exclusion of all possible differentials among those who did not carry a mutation in any of the targeted genes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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