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Letter to the Editor

Variable Genotype Means Variable Phenotype in Myotonic Dystrophy Type 1

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Letter to the Editor

We read with interest the article by Kosta *et al*. about a case study of three patients with Myotonic Dystrophy Type 1 (MD1) with different genetic backgrounds and variable clinical presentation [1]. Patient 1 was an 11-year-old male patient with 900 CTG repeats, who manifested with myopathy, myotonia, and cognitive decline; Patient 2, a 25-year-old male patient with 650 CTG repeats, who manifested phenotypically with myopathy, myotonia, and respiratory insufficiency; and Patient 3, a 40-year-old male patient with 150 CTG repeats, who manifested with mild myopathy and myotonia [1]. It was found that the severity of symptoms increases with the number of CTG expansions and that there is variability in the clinical presentation and severity of DM1 across different age groups and genetic profiles [1]. The study is appealing, but some points require further explanation.

First, the family history was not thoroughly documented [1]. Since the inheritance pattern of the disease is autosomal dominant and MD1 can manifest with anticipation, it is crucial that all first-degree relatives be clinically examined for subtle phenotypic manifestations and genetically tested for the number of CTG repeats using Southern blot or TR-PCR. An apparently negative family history for MD1 does not necessarily mean that relatives do not exhibit CTG expansion or clinical manifestations. They may show clinically subtle manifestations such as cataracts, ptosis, hearing impairment, or even no symptoms at all. Because these patients can transmit the disease, it is crucial to identify them to assess phenotypic and mutation segregation, determine whether the size of the CTG repeat expansion has increased or decreased across generations, and ensure optimal genetic counseling.

Second, no long-term follow-up was reported [1]. Since MD1 is a progressive disease with increasing number and severity of organ involvement over time, it would have been essential to document whether the disease course differed among the three patients, as well as their initial clinical presentation. Presumably, the degree of disease progression also varied among the three patients, with greater CTG repeat expansion being associated with faster progression [2].

Third, the three patients were not systematically screened for multisystem involvement. In addition to skeletal muscle and cardiac involvement, MD1 patients may experience cataracts, cognitive impairment, endocrinopathies, gastrointestinal disorders, and kidney disease. Knowing which organs are subclinically or mildly affected is crucial, as early treatment can prevent complications or even premature death.

The fourth point concerns the type of cardiac involvement in Patient-2 (as described in the abstract) and the cause of the respiratory insufficiency [1]. Was the respiratory insufficiency due to cardiac involvement, respiratory muscle involvement, or both? What type of cardiac disease did this patient have? Did he suffer from dilated cardiomyopathy, arrhythmias, or both? Did the ECG show AV block?

The fifth point concerns the cause of the declining academic performance in Patient-1 [1]. Was it due to encephalopathy, epilepsy, cognitive impairment, fatigue, altered mental status, impaired concentration or alertness, or memory problems?

The sixth point concerns the discrepancy in the description of Patient-2. On the one hand, the clinical onset is stated as late twenties, while on the other hand, his age is given as 25 years [1]. This discrepancy should be clarified. It should also be explained why the patient was described as having the classic phenotype, even though he only presented with myopathy, myotonia, and respiratory insufficiency. The classic phenotype also includes a myopathic face, hearing loss, baldness, ptosis, diabetes, and fatigue.

The seventh point relates to the recommendation that MD1 patients should undergo whole exome sequencing (WES) to rule out differential diagnoses [1]. Although double mutations can occur in MD1 patients, they are extremely rare. Therefore, if abnormal CTG repeat expansion is detected in combination with a corresponding phenotype, no further genetic testing is

required. WES should only be performed if a double mutation is suspected. Were pathogenic variants in genes other than the DMPK gene detected by WES in any of the three patients?

In summary, after confirmation of the diagnosis, MD1 patients require prospective screening for subclinical or mild multisystem disorders, as well as clinical and genetic family screening to assess the clinical and genetic segregation of the disease.

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