Clinical Reasoning:

A case of ataxia, seizure, and choreoathetosis in a 34-year-old woman

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SECTION 1

A 34-year-old woman of Chinese Han descent was admitted to the neurology department after complaining of gait instability for 20 years and seizure attacks for 6 years. At age 14, she began experiencing slurred speech and unsteady gait. Meanwhile, she had learning difficulties and her academic performance was poor. Since then, her intelligence regressed gradually. At age 28, she developed recurrent generalized tonic-clonic seizures and myoclonus refractory to valproic acid and oxcarbazepine. She developed choreoathetosis at age 29. In the following years, the seizures and choreoathetosis progressively worsened. Two years later, she could no longer walk independently due to postural instability caused by ataxic gait. Concurrently, she presented with mild cognitive impairment and memory loss. Medical, birth, and family histories

were noncontributory; no other family members were known to be affected.

Physical examination revealed recent memory decline and calculation decrement, and the Mini-Mental State Examination score was 22/30. The patient had mild dysarthria, prominent instability of gait, and marked truncal and limb ataxia and choreoathetosis, involving the neck, trunk, and all 4 limbs. Decreased muscle tone was detected in both arms and legs. Myoclonic jerks in the trunk and 4 limbs could occasionally be noted (video on the *Neurology*[®] Web site at Neurology.org).

Questions for consideration:

1. In which areas could you localize possible lesions?
2. What is your initial approach to investigation?

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SECTION 2

Generalized tonic-clonic seizures indicate that the cerebral cortex is affected. The occurrence of myoclonus indicates several origins, usually from the cerebral cortex; however, it can also originate from subcortical structures or from the brainstem. Cognitive decline, including memory loss and dyscalculia, is suggestive of cerebral cortex or hemisphere involvement and

may include the hippocampus and the temporal and parietal lobes. Positive Babinski sign is suggestive of pyramidal tract involvement and may originate from cerebral white matter or from the lateral funiculus of the spinal cord. Dysmetria on the finger-to-nose test, limb ataxia, and decreased muscle tone indicate cerebellum or peripheral nerve involvement. However, the muscle strength was normal and no sensory impairment or muscular atrophy were present; thus, peripheral nerve involvement could be excluded. Marked choreoathetosis is suggestive of extrapyramidal involvement and the red and subthalamic nuclei and the globus pallidus lateralis may be involved. These symptoms and signs indicate the involvement of multiple structures of the CNS. The onset in the patient was insidious, and aggravated progressively, indicating the involvement of a genetic or metabolic neurodegenerative disorder.

Laboratory examinations, including blood electrolytes and lactate, as well as liver, kidney, and thyroid function, ceruloplasmin level, antinuclear antibodies profile, and urine metabolic screening, were normal. The CSF examination was normal. Neither corneal Kaiser-Fleischer ring nor cherry-red spot or macular degeneration was found on fundus examination. A small amount of sharp waves, sharp and slow complex waves, were shown in the bilateral frontal, occipital, parietal, and temporal lobes. Cerebral MRI revealed moderate generalized brain atrophy, especially in the cerebellum and brainstem (jamanetwork.com/journals/jamaneurology/fullarticle/780763; figure).

Questions for consideration:

1. What would you consider in the differential diagnosis?
2. What further tests are indicated to narrow down the differential diagnosis?

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Figure Brain MRI

(A) Axial T2 images show moderate generalized brain atrophy; the third ventricle is substantially enlarged. (B, C) Axial T2 images show brainstem atrophy. An enlarged cisterna interpeduncularis and fourth ventricle are shown in B and C, respectively. (D) Sagittal T1 images show cerebellum atrophy.

SECTION 3

The presenting features of the patient, including epilepsy/myoclonus, cerebellar ataxia, choreoathetosis, and cognitive deterioration, could be due to several etiologies. Epilepsy/myoclonus, combined with cerebellar ataxia, and progressive cognitive decline, raise suspicion for progressive myoclonus epilepsies (PMEs). PMEs principally include Lafora disease, neuronal ceroid lipofuscinoses, myoclonic epilepsy with ragged-red fibers (MERRF), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and sialidosis. Muscle biopsy of the left biceps brachii appeared normal. We did not find ragged-red fibers or excess of mitochondria in smooth muscle and endothelial cells of intramuscular blood vessels in the muscle biopsy. In addition, the blood lactate level of the patient was normal. Therefore, MERRF and MELAS were excluded. The fundus examination was normal, so sialidosis was not considered. Choreoathetosis is not a common manifestation of PMEs. Other causes of ataxia with chorea were

considered, including hereditary chorea and spinocerebellar ataxia (SCA).

Chorea of a hereditary etiology is primarily present in Huntington disease (HD), HD-like (HDL) disorders (including HDL1 and HDL2), chorea-acanthocytosis (ChAc), and dentatorubral-pallidoluysian atrophy (DRPLA). Interestingly, seizures can occur in most hereditary disorders involving chorea except HDL2; thus, diagnosis of HDL2 was less likely. Ataxia is not commonly seen in HD, thus, the probability of the patient having HD was relatively small. We did not find acanthocytes in the blood smear of the patient, so ChAc was excluded. Cerebellar ataxia is a prominent feature of any of the over 20 subtypes of SCA. Among those subtypes, SCA type 17 (SCA17) is characterized by ataxia, dementia, and involuntary movements, including chorea and dystonia.

Questions for consideration:

1. What further tests are indicated to narrow the differential diagnosis?
2. What is the final diagnosis?

GO TO SECTION 4

SECTION 4

The combination of chorea/choreoathetosis, dementia, dysarthria, and epilepsy may occur in HD, DRPLA, and SCA17; but cerebellar ataxia is not a common symptom of HD. Subsequently, we carried out genetic testing for HD, DRPLA, and SCA17. Cytosine-adenine-guanine (CAG) triplet repeats analyses were carried out in the *TBP*, *ATN1*, and *IT15* genes. Expansion of CAG in those genes would lead to SCA17, DRPLA, or HD, respectively. CAG triplet repeats of the *TBP* and *IT15* genes were within the normal range; however, expanded CAG repeats (64 repeats) in the one allele of *ATN1* were detected. Therefore, the patient was eventually diagnosed with DRPLA. Haloperidol was administered for the choreoathetosis and levetiracetam and clonazepam for the epilepsy and myoclonus; the choreoathetosis and epilepsy/myoclonus have been partially alleviated.

DISCUSSION DRPLA is a rare neurodegenerative disorder of autosomal dominant inheritance, clinically characterized by ataxia, myoclonus, epilepsy, choreoathetosis/chorea, progressive intellectual deterioration, and psychiatric disturbance. It has been reported to occur predominantly in the Japanese population.¹ The clinical presentation varies depending on the age at onset. Juvenile-onset patients usually exhibit PME, characterized by progressive ataxia, seizures, myoclonus, and dementia, while patients with onset after age 20 tend to develop choreoathetosis/chorea, cerebellar ataxia, and intellectual deterioration.¹ A heterozygous pathogenic CAG trinucleotide expansion in the *ATN1* gene has been confirmed as the cause of DRPLA. The CAG repeat length in individuals with DRPLA ranges from 49 to 88.² Combined degeneration of the dentatorubral and pallidoluysian systems are the major neuropathologic changes.

Our patient exhibited marked progressive cerebellar ataxia, choreoathetosis, combined with myoclonus, epilepsy, and cognitive decline. A diagnosis of DRPLA was confirmed by genetic testing, although there was no positive family history. Myoclonus and various forms of generalized seizures, combined with ataxia and dementia, are observed in DRPLA; however, PME exhibits a similar phenotype. For chorea, the combination of symptoms may provide some indication for the differential diagnosis: chorea and ataxia can both be present in SCA, DRPLA, and ChAc, while chorea and dementia can both be present in HD, HDL2, DRPLA, and SCA17.^{3,4}

There is no treatment available to prevent disease progression in DRPLA; it may only be treated symptomatically. After 10 years, only 30% of patients with DRPLA are able to walk autonomously.¹ Aspiration pneumonia is a common complication in the late

stage of the disease. However, accurate diagnosis is important for prognosis and genetic counseling. As an autosomal dominant inheritance disease with almost full penetrance, DRPLA is characterized by prominent anticipation with strong parental bias, and the clinical presentation is thought to strongly correlate with the expanded CAG repeat size. Size of the CAG repeat transmitted to the offspring depends on the size of the parent's repeat and the sex of the transmitting parent. A much larger intergenerational increase was observed for paternal transmission (5.8 ± 0.9 repeat units/generation) compared to maternal transmission (1.3 ± 1.6 repeat units/generation).^{5–8} More prominent genetic anticipation (26–29 years/generation) due to paternal transmission was revealed, compared to maternal transmission (14–15 years/generation).¹ If any family member is known to have DRPLA, genetic analysis for the disease could be part of the necessary prenatal testing in pregnancy.

AUTHOR CONTRIBUTIONS

Fei Xiao: acquisition of data, study concept and design, writing of the manuscript. Xue-feng Wang: study concept and design, critical revision of manuscript for intellectual content.

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DISCLOSURE

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