INTRODUCTION
Machado-Joseph disease (MJD) is a progressive multi-system neurodegenerative disease, as well as the most commonly inherited spinocerebellar ataxia. In MJD, pyramidal tract signs are present at an anatomical level along with brainstem abnormalities, lower motor neuron symptoms, and ataxia. There is also a marked degeneration of the vestibular system, which is thought to explain the frequent impairment of the vestibulo-ocular reflex, as well as the impaired optokinetic nystagmus that is found in MJD cases. Cases with MJD are most commonly characterised by ophthalmological and neuro-ophthalmological features, such as diplopia, gaze-evoked nystagmus, abnormal saccades, decrease in smooth pursuit gain, impaired vestibulo-ocular reflex, and supranuclear vertical gaze palsy.

Hence, considering that MJD is characterised by heterogeneous phenotypic outcomes, this report highlights the reliability of ophthalmological features for MJD diagnostic purposes. It is important to note that in addition to the degeneration of the several systems mentioned above, MJD symptoms may also include parkinsonian features; however, these are rare.

CASE REPORT

Case 1: A 45-year, right-handed female presented with difficult ambulation for 7 years. As time progressed, she developed speech problems and deterioration in gait. Furthermore, she reported constipation, numbness and tingling in her feet. On examination, it was discovered that she had spastic dysarthria, bradykinesia, mild facial weakness on the left side, moderate spasticity of all 4 limbs, and a wide-based gait involving a scissors-like pattern of movement. She had bilateral esotropia causing both of her eyes to point inwards. She also displayed gaze-evoked nystagmus in the horizontal direction, giving rise to involuntary movement of the eyes when trying to look to her left or right. She also had difficulty in reading and watching television due to intermittent tonic contractions of the orbicularis oculi and procerus on both sides. Exposure to the sun easily exacerbated this problem. Furthermore, she had difficulty opening her eyes at times, characteristic of blepharospasm. Among ten siblings, she and her two brothers, along with their mother, were also affected by MJD. She had two healthy children. DNA testing for CAG (cytosine, adenine, guanine) repeat expansion was completed and shown to be consistent with MJD. T1-weighted MRI revealed marked amounts of cerebellar, pontine, and temporal lobe atrophy (Figure 1).

Case 2: A 60-year right-handed female presented with difficulties in walking, balance, and action tremors in both upper extremities. She eventually became wheelchair-bound and also developed speech problems. Eleven of her thirteen siblings exhibit similar symptoms as hers. On examination, besides spastic dystarthis, finger, nose, dysmetria, diffuse spasticity of the limbs, and slow rapid alternating movements, her primary ophthalmological symptom were that of horizontal jerk nystagmus when gazing to each side. This resulted in complaints of unclear image forming. Other ophthalmological issues found to be mutually shared between the patients included bilateral esotropia,
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as well as the twitching of the eyelids due to the intermittent contractions of the orbicularis oculi. Sensory testing proved to be normal. DNA testing for CAG repeat expansion confirmed the presence of MJD. T1-weighted MRI displayed significant atrophy within the cerebellum and frontal lobe (Figure 2).

DISCUSSION

Although MJD shares numerous features with other inherited neurodegenerative disorders, there are more particular disease features that facilitate the accurate identification of MJD. It is these particular disease features and their strong phenotypic heterogeneity that has allowed for the classification of MJD into three or four different clinical subtypes. Patients in the type-I class show pyramidal signs and extra-pyramidal signs, like dystonia. Cerebellar and pyramidal signs characterise type-II patients, whereas type-III consists of those with cerebellar signs and peripheral neuropathy. Finally, type-IV patients develop more parkinsonian features and distal amyotrophy. Ophthalmoplegia and problems with vision are found to be frequent throughout all subtypes of MJD. However, nuclear ophthalmoplegia is found to be more common in type-I MJD patients while supranuclear ophthalmoplegia is more common in MJD type-III patients. Since minor but more specific features such as erythropoietin (EPO) are of major importance for clinical diagnosis of MJD, this study stresses that greater emphasis should be placed on subtle clinical aspects of ophthalmological features when diagnosing MJD.

While there are a few marked differences in the two cases presented here, there was a novel overlap pertaining to the ophthalmological features. Both patients seem to share nystagmus in the horizontal direction and orbicularis oculi contraction. Other features that were common between the two cases include bilateral esotropia. The oculomotor symptoms found in these patients were very similar to previous case reports, which also reported difficulties with balance and gait alongside ophthalmoplegia and contractions of the orbicularis oculi; especially, when attempting to voluntarily open the eyes. Prior research has alluded to the neurodegenerative processes of the central vestibular system to help explain the impaired optokinetic nystagmus, vestibulo-ocular reaction, and horizontal gaze holding present in MJD cases. Several recent studies also suggest that the cognitive symptoms of MJD stem from the degeneration of visual cortical processing. Prior research has also mentioned the use of procedures such as eyeblink conditioning; albeit with caution, to assist in drawing conclusions regarding cognitive symptoms in MJD.

It is also important to note the different genetic profiles for the two cases. In the first case, her mother and two out of ten siblings suffer from MJD. In the second case, however, eleven of the thirteen siblings were affected, suggesting a stronger genetic predisposition. Variability in the phenotypic outcomes within families with MJD suggests that although MJD is caused by a single major gene, it is modulated by modifier factors. There is no existing neuropathological studies that specifically address the question of the degree to which cerebellar structures involved in eye-movements are affected in mutations related to MJD. This paper highlights the importance of future research on the genetic basis of ophthalmological features and their implications on MJD. It is interesting to note that parkinsonian features were also diagnosed among the two cases, particularly bradykinesia in the first case and action tremor and dysmetria in the second. Further research should investigate whether, there exists a link between parkinsonism and MJD.

Figure 1: (Case 1) Axial view of brain MRI, FLAIR image showing marked atrophy of cerebellum (spear), pons (filled arrow head), and temporal lobes (outlined arrow head).

Figure 2: (Case 2) Sagittal view of brain MRI, T1-weighted image showing marked cerebellar atrophy (lines).
For the proper management and diagnosis of MJD, authors emphasise the precise identification of the ophthalmological features frequently associated with this rare autosomal dominant condition.

REFERENCES


