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Pathological findings of anti-Yo cerebellar degeneration with Holmes tremor

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Holmes tremor, also known as rubral tremor, is defined as the combination of rest, action and postural tremor in the upper extremities with the frequency around 4.5 Hz.¹ Involvement of dentato-rubro-thalamic and/or nigrostriatal pathways have been considered contributory to the clinical manifestation,¹ and the localisation of Holmes tremor was determined primarily based on the neuroimaging studies.² To our knowledge, no detailed postmortem examinations were reported in Holmes tremor. Here, we present the pathology of a case with Holmes tremor associated with anti-Yo cerebellar degeneration.

CASE REPORT

A woman in her eighth decade developed subacute onset of gait ataxia and dysarthria within 6 months. She required a walker to ambulate and needed assistance in her daily living. Four months after the symptom onset, she developed upper extremity tremor and head tremor. Neurological examination revealed square wave jerks, nystagmus on lateral gaze, broken smooth pursuit and scanning speech. She had marked cerebellar ataxia with dysmetria on the bilateral finger-to-nose tests and heel-shin slides. She also had truncal titubation. She had rest head tremor. She also had rest, postural and action tremors in her upper extremities, and the tremor became coarse and irregular with goal-directed movements, typical of Holmes

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tremor. She did not have any voice tremor or leg tremor. She had normal muscle strength, reflexes and sensory examinations. She had an elevated serum anti-Yo antibody titre of 1:61440. No malignancy was found in the computer tomography of the chest, abdomen and pelvis. Mammography did not reveal any evidence of tumours. MRI of the brain showed mild cerebellar atrophy. She underwent hysterectomy with bilateral oophorectomy 6 months after the symptom onset and subsequently her anti-Yo antibody titre decreased to 1:7680. However, no gynaecologic tumour was identified in the pathological examination of the samples removed surgically. She did not have further worsening in her cerebellar ataxia, and her Holmes tremor persisted with the same severity. She passed away 17 years later due to aspiration pneumonia.

On postmortem examination, the cerebellum was atrophic (figure 1A), more prominent in the vermis than in the hemispheres. There was subtotal loss of Purkinje cells and severe Bergmann gliosis (figure 1B), and numerous empty baskets (figure 1C) and severe myelin loss of the foliae and album cerebelli. There was moderate neuronal loss in the dentate nucleus with reactive gliosis (figure 1D). The red nucleus had scattered atrophic neurons and mild gliosis (figure 1E). There was severe neuronal loss in the inferior olivary nucleus (ION) (figure 1F) with loss of myelin in the amiculum or central tegmental tract, hilus and olivocerebellar fibres. The pontine nuclei included scattered atrophic neurons; however, the white matter tracts were unremarkable. Both parts of the substantia nigra (SN), thalamus and striatum were apparently normal.

DISCUSSION

In Holmes tremor, disruption of dentato-rubro-olivary tract is the proposed mechanism primarily based on structural lesions such as ischaemic or haemorrhagic strokes, cysts, vascular malformations, trauma and tumours in the neuroimaging studies.¹ Lesion sites involve red nucleus, rubrothalamic tracts, central tegmental tracts (rubro-olivary tracts) and superior cerebellar peduncles, which constitute rubro-olivary-cerebellar-thalamic loops. In our case, we found neuronal loss in the red nucleus, ION, cerebellar cortex and dentate nucleus, which provide the direct pathological evidence of previously hypothesised Holmes tremor localisation based on neuroimaging studies.

In our case, we did not identify any gynaecological tumours and it is possible that she had non-paraneoplastic anti-Yo encephalitis, which have been described.³ Alternatively, she might have occult ovarian malignancy since she had a remarkable decrease of the antibody titre and the stabilisation of cerebellar ataxia after surgery, and long-term survival.

Only few studies on anti-Yo paraneoplastic cerebellar degeneration (PCD) pathology have been reported.⁴ Typical anti-Yo PCD pathological findings showed prominent Purkinje cell loss⁴ and cerebellar cortical atrophy,⁴ which account for the clinical presentation of cerebellar ataxia, but none of these reported cases had Holmes tremor presentation. Occasionally, Holmes tremor can occur in anti-Yo PCD cases.⁵ Compared with the pathology of anti-Yo PCD cases without Holmes tremor, our case demonstrated additional pathology in the red nucleus, dentate nucleus and ION, which could be contributory to the Holmes tremor phenotypes. Alternatively, these pathological findings could indicate the

consequences of long-term exposures to rhythmic hyperexcitable tremor loops in these brain regions. In addition, the preservation of striatum and SN in our case might argue against the necessity of nigrostriatal involvement in Holmes tremor.² In conclusion, we reported pathological findings of Holmes tremor associated with anti-Yo cerebellar degeneration and our findings suggested that red nucleus, cerebellum and ION could be important for the pathogenesis of Holmes tremor.

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Figure 1.

(A) On gross examination, the brunt of the cerebellar atrophy involves the upper vermis and adjacent parts of the hemispheres. (B) Micrographs show subtotal loss of Purkinje cell loss with severe Bergmann gliosis (Luxol fast blue H&E [LH&E], 200 $\times$), (C) empty baskets (Bielshowsky, 400 $\times$), (D) moderate neuronal loss and reactive gliosis involving the dentate nucleus (LH&E, 400 $\times$), (E) scattered atrophic neurons with mild gliosis involving the red nucleus (LH&E, 400 $\times$), (F) severe neuronal loss involving the inferior olivary nucleus with myelin loss of the amiculum or central tegmental tract (upper-left corner) and of the hilus (lower-right corner) (LH&E, 200 $\times$).