Adult Onset Sporadic Cerebellar Ataxia in Singapore: Diagnostic Outcomes of Paraneoplastic Antibody Testing and Early Clinical Features of Paraneoplastic Cerebellar Degeneration

Dear Editor,

The initial presentation of cerebellar ataxia remains a diagnostic challenge due to its multiple etiologies, one of which is paraneoplastic cerebellar degeneration (PCD), a rare neurological disease. Although paraneoplastic antibody testing may be helpful, seronegative PCD may account for up to 50% of PCD cases.[1]

The causes of ataxia in the Asian population differ from that of the Western population – the proportion of multiple system atrophy of the cerebellar type (MSA-C) relative to MSA with predominant parkinsonism (MSA-P) is higher[2] and Friedrich's ataxia is rare.[3] MSA-C can be difficult to diagnose at onset. In patients whose etiology cannot be determined, a diagnostic label of either idiopathic adult onset cerebellar ataxia (AOCA) or idiopathic late onset cerebellar ataxia (ILOCA) is usually applied. However, it is not uncommon for the etiology to remain unknown despite extensive investigations.[4]

This study aimed to determine the diagnostic outcomes in adult patients presenting with a subacute or chronic cerebellar ataxia for which the diagnosis was not readily apparent, thus, requiring paraneoplastic antibodies to be performed. We also investigated clinical features at onset that would allow us to distinguish PCD from sporadic degenerative ataxias.

Materials and Methods

A retrospective case note analysis was performed on patients referred to the National Neuroscience Institute between 1 January 2007 and 1 October 2014 who presented with a subacute or chronic progressive ataxia and had anti-neuronal antibodies performed as part of the diagnostic workup. Inclusion criteria included disease onset after the age of 20 years, absence of established symptomatic causes such as ischaemia, haemorrhage or tumour in the posterior fossa, alcohol abuse and chronic anticonvulsant use. Patients were excluded if there were other dominant neurological signs. Paraneoplastic antibodies that were tested included: Hu, Yo, Ri, CV2, amphiphysin, Ma2, Tr (EUROIMMUN and EUROLINE kits, EUROIMMUN AG, Luebeck, Germany). A subset of patients was also tested for voltage-gated calcium channel (VGCC) antibody and voltage-gated potassium (VGKC) antibody. The metabotropic glutamate receptor 1 (mGluR1) antibody was not tested.

Diagnoses of MSA-C, SAOA or ILOCA and PCD were made based on established clinical criteria.[4-6]

Ethical approval was obtained from the SingHealth Centralised Institutional Review Board.

Results

A total of 81 patients (48 male and 33 female) presented with a cerebellar syndrome which required further diagnostic workup. The anti-Yo antibody was positive in 3 (3.7%) patients. Four (4.9%) patients were diagnosed with PCD. The diagnostic outcomes are shown in Table 1.

The 4 patients diagnosed with PCD were between the ages of 60 and 75 with a mean age of 66 years and were

Table 1. Diagnostic Outcomes of Patients Presented with Subacute or Chronic Progressive Ataxia with Paraneoplastic Antibodies Testing Performed

Diagnosis	Number of Patients (n = 81)
MSA-C	20 (24.7%)
AOCA or ILOCA	9 (11.1%)
Infectious causes	6 (7.4%)
Paraneoplastic cerebellar degeneration	4 (4.9%)
Spinocerebellar ataxia	3 (3.7%)
SREAT	3 (3.7%)
Drug-related diagnoses	2 (2.5%)
Other diagnoses: cervical myelopathy, CADASIL, corticobasal degeneration, dementia, hypertrophic olivary degeneration, Issac's syndrome, limbic encephalitis, lumbar spondylosis, Parkinson's disease, progressive supranuclear palsy, sensory ataxia, Sjogren's syndrome and vestibulopathy	20 (24.7%)
Unexplained diagnoses	14 (17.4%)

AOCA: Adult onset cerebellar ataxia; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; ILOCA: Idiopathic late onset cerebellar ataxia; MSA-C: Multiple system atrophy of the cerebellar type; SREAT: Steroid-responsive encephalopathy associated with autoimmune thyroiditis

followed up for a mean of 2.67 years. Ovarian cancer was detected in 3 female patients who were anti-Yo antibody-positive patients while small cell cancer of the lung was detected in 1 male patient who was antibody negative. In all cases, malignancy was detected on the same clinical encounter with normal brain imaging at onset. All received intravenous immunoglobulin and chemotherapy with 1 patient also receiving intravenous methylprednisolone. Treatment response was poor; the patients required the use of a walking aid and wheelchair after a mean of 7 and 29 months, respectively. The last known functional status of these 4 patients was 1 was wheelchair bound, 1 required a walking aid, 1 was independent and 1 whose status was unknown. At the end of the follow-up period, only 1 patient (25%) remained alive.

A total of 29 patients, between the ages of 33 and 81, with a mean age of 63 years, were diagnosed with sporadic degenerative ataxias (MSA-C, AOCA and ILOCA); 14 (51.7%) were female. Brain imaging findings at onset include 16 (55.2%) with cerebellar atrophy, 8 (27.6%) were normal and 5 (17.2%) with non-specific changes. None had the hot cross bun sign seen initially. These patients required the use of a walking aid and wheelchair after a mean of 34.8 and 36 months, respectively. Six (20.7%) were wheelchair bound, 8 (27.6%) required a walking aid and 15 (51.7%) remained independent on the last follow-up. Twenty-six (89.7%) patients with sporadic degenerative ataxias remained alive at the end of the follow-up period.

Clinical features at onset in patients with PCD are compared with those with sporadic degenerative ataxias in Table 2. Statistical analyses were not performed due to small patient numbers.

Table 2. Comparison of the Prevalence of Clinical Features Seen at the Onset of PCD and Sporadic Degenerative Ataxias

	Paraneoplastic Cerebellar Degeneration (n = 4)	**Sporadic Degenerative Ataxias (n = 29)**
Cerebellar features		
Nystagmus	0 (0%)	8 (27.6%)
Dysarthria	1 (25%)	13 (44.8%)
Intention tremor	2 (50%)	19 (65.5%)
Gait ataxia	1 (25%)	22 (75.9%)
Truncal ataxia	3 (75%)	1 (3.4%)
Positive Romberg's	0 (0%)	4 (13.8%)
Extrapyramidal features		
Parkinsonism	0 (0%)	10 (34.5%)
Dystonia	0 (0%)	0 (0%)
Autonomic features		
Autonomic dysfunction	0 (0%)	8 (27.6%)
Urinary incontinence	0 (0%)	2 (6.9%)
Orthostatic hypotension	0 (0%)	6 (20.7%)
Erectile dysfunction	0 (0%)	1(3.4%)
Other features		
Cognitive impairment	0 (0%)	2 (6.9%)
Cranial nerve involvement	0 (0%)	1 (3.4%)
Motor symptoms	0 (0%)	3 (10.3%)
Sensory symptoms	1 (25%)	1 (3.4%)

PCD: Paraneoplastic cerebellar degeneration

Discussion

In patients presenting with a cerebellar syndrome for which the initial diagnosis was unclear and paraneoplastic antibody testing was performed, 4 cases of PCD were detected, of which 3 were positive for the anti-Yo antibody. We detected only 1 case of seronegative PCD. In all 4 cases, the primary tumour was detected in the same clinical encounter. This was in contrast to previous studies where the majority of PCD cases either occurred before the eventual diagnosis of cancer, or occurred in patients with a known history of cancer.[7,8] In this study, the number of PCD cases was underestimated as patients with known malignancies under regular surveillance by the oncologists tend not to have further confirmation of PCD with antibody testing.

There has not been any previously published study investigating the yield of antibody testing in patients presenting with a cerebellar syndrome. Our pick-up rate of 3.7% is high for this rare disease. Previous studies screening for a broad range of paraneoplastic disorders had a much lower pick-up rate – in a study by Shams'ili et al, more than 5000 samples were screened, of which 137 patients were antibody positive.[8] However, the population screened was heterogeneous with a range of clinical presentations.

The most common diagnostic outcome was MSA-C (24.7%). Our findings are consistent with other studies performed in the Western population where MSA-C remains a common diagnosis in patients initially thought to have sporadic adult onset ataxia.[9] The high proportion of patients with unexplained ataxia in our study is consistent with a previous study.[9] Although extensive genetic testing was not performed in our local context, it is unlikely that this would alter the proportion of cases with unexplained ataxia as further genetic testing in this population is low yield.[10]

Early clinical features that favoured a diagnosis of PCD over sporadic degenerative ataxias included the female gender, rapidly progressive symptoms, normal brain imaging at onset, truncal ataxia, absence of nystagmus, dysarthria, parkinsonism and autonomic features, which are

consistent with previous studies.[8] Normal brain imaging in the presence of clinically severe disease has been found to be predictive of PCD[11,12] while cases in which brain imaging was abnormal at onset are rare.[13,14] It has been recommended that the diagnosis of PCD must be suspected in all patients with subacute and rapid progression of ataxia.[8] Although disease progression is most rapid in MSA-C amongst other causes of sporadic degenerative ataxias,[15] PCD has a more rapid progression compared to MSA-C.

The limitation of this study was the small patient numbers. This was a real-world study examining the clinical outcomes in patients presenting with subacute or chronic ataxia who had paraneoplastic antibodies tested. However, this could be influenced by individual and institutional practices. Prospective studies examining patients at onset would be helpful. The relatively high pick-up rate of antibody testing underscores the utility of testing such patients for PCD.

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Zheyu Xu, [1]*MBBChir MA, FRACP*, Jinglin Zhang, [1,2]*MD, PhD*, Samuel YE Ng, [1]*BPsych (Hons)*, Josiah YH Chai, [1]*MBBS, FAMS (Neurology), FRCP Edin*, Louis CS Tan, [1]*MBBS, FAMS (Neurology), FRCP Edin*

[1]Department of Neurology, National Neuroscience Institute, Singapore
[2]Department of Neurology, Beijing Ditan Hospital, People's Republic of China

Address for Correspondence: Dr Xu Zheyu, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433. Email: Zheyu_Xu@nni.com.sg