Genotype-phenotype correlations of adult-onset PLA2G6-associated Neurodegeneration: case series and literature review

Yung-Tsai Chu, Han-Yi Lin, Pei-Lung Chen and Chin-Hsien Lin*

Abstract

Background: Phospholipase A2 group VI (PLA2G6) mutations associated with neurodegeneration (PLAN) manifest as heterogeneous neurodegenerative disorders with variable ages of onset. The genotype-phenotype correlation is not well-established. We aim to describe three adult patients with PLAN and combined these data with results from previous studies to elucidate adult-onset PLA2G6 phenotype-genotype correlations.

Case presentations: The first index patient presented with dystonia-parkinsonism starting at age 31 years, accompanied by major depression and cognitive decline. Genetic analysis using targeted next generation sequencing (NGS) panel, Sanger sequencing, and segregation analyses revealed a compound heterozygous mutation, c.991G > T (p.D331Y)/c.1077G > A (M358IfsX), in PLA2G6. The other two patients had levodopa-responsive, early-onset parkinsonism, starting in their late twenties. Both patients had homozygous c.991G > T (p.D331Y) mutations in PLA2G6. Patient characteristics of our reported 3 cases were compared to those of 32 previously described (2008 to 2019) patients with adult-onset PLAN. Among the combined cohort of 35 patients with adult-onset PLAN, 14 had dystonia-parkinsonism, 17 had early-onset Parkinson’s disease, 3 had hereditary spastic paraparesis, and one had ataxia. The c.991G > T (p.D331Y) mutation was almost exclusively found in Chinese patients, suggesting a common founder effect. All patients with homozygous p.D331Y mutations had levodopa-responsive, early-onset PD (100%); while other mutations mostly led to dystonia-parkinsonism, ataxia, spasticity, and combine psychiatric comorbidities.

Conclusions: We showed that adult-onset PLAN could present as purely parkinsonism features, without brain iron accumulation, particularly patients with homozygous p.D331Y mutations. Compound heterozygous mutations, including heterozygous p.D331Y, produced heterogeneous phenotypes, without obvious levodopa responsiveness.

Keywords: PLA2G6, Dystonia-parkinsonism, Early-onset parkinsonism, Hereditary spastic paraparesis, Ataxia, PLA2G6-associated neurodegeneration

Background

PLA2G6-associated neurodegeneration (PLAN) is a heterogeneous group of neurodegenerative disorders that result from mutations in the phospholipase A2 group VI gene (PLA2G6) [1, 2]. The PLA2G6 gene encodes a group of VIA calcium-independent phospholipase A2 proteins. Phospholipase A2 is an enzyme involved in phospholipid metabolism, and it is essential for maintaining cell membrane integrity [1, 2]. PLAN can be classified into four subtypes, based on onset age, including: infantile neuroaxonal
dystrophy (INAD), atypical neuroaxonal dystrophy (ANAD), dystonia-parkinsonism, and autosomal recessive early-onset parkinsonism (known as PARK14) [3]. INAD and ANAD onsets occur in childhood. Brain magnetic resonance image (MRI) findings have revealed that most patients have cerebellar cortical atrophy and iron deposition in the globus pallidus and substantia nigra. These findings are known as neurodegeneration with brain iron accumulation, type II (NBIA II) [4]. In contrast to childhood-onset PLAN, adult-onset PLAN is associated with widely variable clinical manifestations, and the genotype-phenotype correlation has not been well established. Here, we describe three patients with adult-onset PLAN. We compared the clinical features, treatment responses, and radiological findings of these patients to those reported for 43 patients described in previous studies to elucidate the phenotype-genotype correlations in adult-onset PLAN.

Case presentation
Patient 1 was a 36-year-old man, with normal birth and developmental milestones. He had a history of depression for 18 years but had not used anti-depressant or neuroleptic agents consistently. Several times, suicide was attempted. At age of 31 years, motor symptoms gradually developed. He had progressive onset of spastic dysarthria and hypophonia, predominantly left-sided bradykinesia, and dystonia in the left hand ensued. Three years after the onset of motor symptoms, he was confined to a wheelchair with anarthria, and he was totally dependent on assistance from others in daily living activities. In addition, he experienced several episodes of oculogyric crisis. He did not have a relevant family history (Fig. 1a).

He was then brought to our movement disorder clinic for evaluation at the age of 36 years. The neurological examination revealed oromandibular, truncal, and limb dystonia and generalized rigidity and bradykinesia; the part III motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) was 60 out of 108. He scored 21 out of 30 on the Mini-Mental State Examination (MMSE). There were no Kayser-Fleischer rings during the physical examination. A brain MRI showed diffuse cortical and cerebellar atrophy, with no abnormal iron deposits in the basal ganglia (Fig. 2a-c). A Tc-99 m TRODAT single-photon emission computed tomography scan revealed markedly reduced dopamine transporter activity in the bilateral basal ganglia (Fig. 2d). 18F-labeled fluoro-deoxyglucose positron emission tomography (FDG-PET) scan demonstrated hypometabolism in the bilateral parieto-occipital lobes. The patient was treated with levodopa (400 mg per day) and benserazide (50 mg three times per day), a rotigotine transdermal patch (8 mg per day), and clonazepam (0.5 mg). These medications improved motor function to the extent that he could walk with assistance, and the UPDRS part III motor score was 40 out of 108 after treatment.

The results of laboratory tests were within normal limits, including normal plasma ceruloplasmin levels and 24-h urine copper excretion. We then performed comprehensive genetic analyses for the index patient with a capture-based next generational sequencing targeted gene panel that covered more than 40 genes related to Parkinson’s disease (PD) and neurodegenerative disorders using similar methods described previously [5]. Mutations were verified with Sanger sequencing and dye-
terminator chemistry in an Automated Sequencer Genetic Analyzer (model 3100; Applied Biosystems, Foster City, CA, USA). We identified the pathogenic missense variant, c.991G > T (p.D331Y), and a c.1077G > A (M358IfsX) frame-shift mutation in PLA2G6 (Fig. 1b,c).

Direct Sanger sequencing verified the c.991G > T (p.D331Y) missense mutation in both the proband and the asymptomatic mother (Fig. 2a,b). The c.1077G > A (M358IfsX) frame-shift mutation in PLA2G6 was confirmed with Sanger sequencing in both the proband and the asymptomatic father (Fig. 2a,c). We then confirmed that the proband had compound heterozygosity, with the mutations in a trans configuration.

Patient 2 was a 48-year-old woman presented with progressive shuffling gait and decreased right arm swing since age of 30 years. Right-sided rigidity and bradykinesia were noted later. PD was diagnosed, and she responded well to levodopa. She had prominent psychiatric symptoms, including anxiety, depression and paranoid delusions, which symptoms occurred soon after the onset of right-side limbs slowness. Brain MRIs did not show structural lesions. A Tc-99 m TRODAT scan reveals reduced dopamine transporter activity in the bilateral basal ganglia.

Patient 3 was a 34-year-old woman that started to complain of right-leg clumsiness at the age of 26 years. Right-arm clumsiness and gait disturbances followed 2 years later. Levodopa and dopamine agonists were given, with good motor responses; however, motor fluctuations and levodopa-induced dyskinesia developed 5 years after starting the medications. Depression and anxiety were also noted. Brain MRIs showed no structural change and the MMSE score was 28 out of 30 while she was 36 years old. A genetic analysis with a targeted NGS panel identified a homozygous c.991G > T (p.D331Y) mutation in PLA2G6.

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Systematic review of previous reports of patients with PLAN

We searched the PubMed database for all English literature that had the terms: “PLA2G6 mutation” or “phospholipase A2 group VI gene mutation”. We
selected case reports or case series of patients with genetically confirmed PLAN, published in 2008–2019. Patients with childhood onset were excluded. We selected patients with adult-onset PLAN (onset age older than 18 years) and affected family members within the same family. However, family members with onset age less than 18 years were excluded. We summarized the clinical, genetic, and imaging characteristics of different genotypes to elucidate adult-onset PLA2G6.

We identified 32 patients from 23 articles that described patients with adult-onset PLAN. We did not enroll patients with onset age less than 18 years old. Including our three patients, we analyzed data for 35 patients. The clinical characteristics and genetic findings are summarized in Table 1 [1–3, 6–32]. The mean age of onset was 26.3 ± 8.6 years. The mean age of examination was 30.4 ± 5.5 years. At the initial presentation, 10 patients (28.6%) had neuropsychiatric symptoms in-
### Table 1 Clinical, genetic, and imaging characteristics of patients with genetically confirmed adult-onset PLAN in the literature

| Author, year, Patient Gender, Ethnicity | Genotype Type | Sex | AAO | Initial symptoms | Main symptoms during examination | MRI |
|----------------------------------------|---------------|-----|-----|------------------|----------------------------------|-----|
| **Homozygous p.D331Y mutations (N = 5)** |               |     |     |                  |                                   |     |
| Shi et al. 2011 [6] P1 Chinese Homo c.991G > T (p.D331Y) | EOPD M 37 | Gait disturbance | + – – – – nl |
| Xie et al. 2015 [7] PA Chinese Homo c.991G > T (p.D331Y) | EOPD M 36 | Gait disturbance | + – – – – nl |
| PB Chinese Homo c.991G > T (p.D331Y) | EOPD M 36 | Right hand tremor | + – – – – nl |
| This study P2 Chinese Homo c.991G > T (p.D331Y) | EOPD F 30 | Slowing gait | + – – – D, P, A nl |
| This study P3 Chinese Homo c.991G > T (p.D331Y) | EOPD F 26 | Right leg clumsiness | + – + – D, A nl |
| **Compound heterozygous p.D331Y/ other mutations (N = 5)** |               |     |     |                  |                                   |     |
| Lu et al. 2012 [8] P3 Chinese Compound hetero c.991G > T (p. D331Y)/ c.1077G > A (M358IfsX) | DP F 19 | Unsteadiness and bradykinesia | + + – + P,C CoA, CeA |
| Chen et al. 2018 [9] P3 Chinese Compound hetero c.991G > T (p. D331Y)/ c.1982C > T | DP M 29 | Walking difficulty | – – – + CeA |
| This study P4 Chinese Compound hetero c.991G > T (p. D331Y)/ c.2218G > A (p.G740R) | HSP M 31 | Gait disturbance | – – + + CeA |
| Ji et al. 2019 [10] P1 Chinese Compound hetero c.991G > T (p. D331Y)/ c.1648delC | Ataxia F 30 | Imbalance | – – + + D CeA |
| This study P1 Chinese Compound hetero c.991G > T (p. D331Y)/ c.1077G > A (M358IfsX) | DP M 18 | Depression and psychosis | + + – – D, P, C CoA, CeA |
| **Homozygous Mutations other than p.D331Y (N = 17)** |               |     |     |                  |                                   |     |
| Paisa'n-Ruiz et al., 2008 [3] P1 of F1 Indian Homo c.2222G > A (p.R741Q) | DP F 26 | Cognitive decline | + + + – D, C CoA |
| P1 of F2 Pakistani Homo c.2239C > T (p.R747W) | DP F 18 | Foot drop | + + + – C CoA |
| Sina et al. 2009 [11] P1 Iranian Homo c.C1894T (p.R632W) | DP M 25 | Foot drop | + + + – C CoA |
| P2 Iranian Homo c.C1894T (p.R632W) | DP M 22 | Foot drop | + + + – C CoA |
| P3 Iranian Homo c.C1894T (p.R632W) | DP F 21 | Foot drop | + + + + C CoA |
| Agarwal et al., 2012 [12] P1 Scandinavian Homo c.G238A (p.A80T) | EOPD F 22 | Depression | + + + – D, A, C I |
| Virmani et al., 2014 [13] P1 Indian Homo c.2222G > A (p.R741Q) | DP F 25 | Depression and psychosis | + + + – D, P CoA |
| P2 Indian Homo c.2222G > A (p.R741Q) | DP F 22 | Depression | + + + – CoA |
| Malaguti et al. 2015 P Italian Homo c.C1547T (p.A516W) | DP F 27 | Stiff legs sensation | + + + – C I |
| Giri et al. 2016 P Turkish Homo c.2239C > T (p.R747W) | EOPD F 27 | Left limb slowness | + – – – D,P,C CoA |
Discussion and conclusions

We described the clinical, genetic, and neuroimaging aspects of three patients with adult-onset PLAN. One patient had compound heterozygous p.D331Y and M358IfsX frame-shift mutations and presented with dystonia-parkinsonism. The other two patients had homozygous p.D331Y mutations and presented with levodopa-responsive early-onset parkinsonism. After identifying more than 20 PLA2G6 mutations in previous reports [1–3, 6–32], we observed that the c.991G > T (p.D331Y) mutation in PLA2G6 was almost exclusively found in Chinese patients, suggesting a common founder effect of this variant in Chinese populations. Moreover, patients with homozygous c.991G > T (p.D331Y) mutations showed purely early-onset parkinsonism features with good levodopa response.
responses. In contrast, patients with other genotypes, including compound heterozygous c.991G > T (p.D331Y) mutations and other variants, predominantly presented with dystonia-parkinsonism and HSP. Our results further support previous studies that PLA2G6 mutations had both clinical and genetic heterogeneity. Moreover, our findings suggested that the c.991G > T (p.D331Y) mutation was a potentially common founder mutation in populations of Chinese ethnicity.

Table 2: Comparison of patients with different clinical subtypes of PLAN

| Characteristics          | Dystonia-Parkinsonism | Early-onset PD | HSP | Ataxia | P-value |
|--------------------------|-----------------------|---------------|-----|--------|---------|
| Age at onset, years      | 21.7 ± 3.9            | 27.2 ± 5.1    | 46.0 ± 23.5 | 30      | 0.10    |
| Age at examination, years| 32.5 ± 4.9            | 33.7 ± 8.1    | N.A. | 31      | 0.26    |
| Sex, male                | 5 (35.7%)             | 10 (58.8%)    | 1 (33.3%) | 0      | 0.38    |
| Main symptoms and signs  |                       |               |      |        |         |
| Parkinsonism             | 14 (100.0%)           | 17 (100.0%)   | 0   | 0      | 1.00    |
| Dystonia                 | 13 (92.8%)            | 2 (11.8%)     | 0   | 0      | < 0.001** |
| Pyramidal sign           | 11 (78.6%)            | 8 (47.1%)     | 3 (100%) | 1      | 0.32    |
| Cognitive decline        | 9 (64.3%)             | 10 (58.8%)    | 1 (33.3%) | 0      | 0.91    |
| Depression/Anxiety       | 4 (28.6%)             | 7 (41.2%)     | 1 (33.3%) | 1      | 0.78    |
| Psychosis                | 4 (28.6%)             | 6 (35.3%)     | 0   | 0      | 0.93    |
| Brain MRI findings       |                       |               |      |        |         |
| Cortical atrophy         | 9 (64.3%)             | 8 (47.1%)     | 0   | 0      |         |
| Cerebellar atrophy       | 3 (21.4%)             | 1 (5.9%)      | 1 (33.3%) | 1      | 0.03*   |
| Hypo-intensity in GP     | 1 (7.1%)              | 1 (5.9%)      | 0   | 0      | 0.98    |

Data are the number (%) or the mean ± SD. PLAN, Phospholipase A2 group VI-associated neurodegeneration; PD, Parkinson’s disease; HSP, hereditary spastic paraparesis; MRI, magnetic resonance imaging; GP, globus pallidus. **P < 0.05; ***P < 0.01. P-values that compare individual characteristics between groups with dystonia-parkinsonism and early-onset PD were evaluated with an analysis of variance. Variables without a normal distribution were compared with the Kruskal-Wallis test, the non-parametric equivalent of the independent sample t-test.

Table 3: Comparison of patients with different PLAN-related genotypes

| Characteristics          | Homozygous p.D331Y mutations N = 5 | Compound heterozygous p.D331Y/other mutations N = 5 | Homozygous Mutations other than p.D331Y N = 17 | Compound Heterozygous mutations other than p.D331Y N = 8 | P-value |
|--------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------------|---------|
| Age at onset, years      | 33.0 ± 4.8                        | 25.4 ± 6.3                                    | 23.2 ± 11.0                                   | 16.8 ± 9.9                                          | 0.23    |
| Sex, male                | 2 (50.0%)                         | 2 (40.0%)                                     | 6 (35.3%)                                     | 5 (62.5%)                                           | 0.41    |
| Ethnicity                |                                    |                                              |                                              |                                                     |         |
| Chinese                  | 5 (100.0%)                        | 5 (100.0%)                                    | 0                                             | 1 (12.5%)                                           | < 0.001** |
| East Asian               | 0                                  | 0                                             | 1 (4.8%)                                      | 4 (50.0%)                                           | 0.01*   |
| South Asian              | 0                                  | 0                                             | 4 (19.0%)                                     | 0                                                   | 0.16    |
| Middle Eastern           | 0                                  | 0                                             | 14 (66.7%)                                    | 0                                                   | < 0.01** |
| Caucasian                | 0                                  | 0                                             | 2 (9.5%)                                      | 3 (37.5%)                                           | 0.11    |
| Main clinical subtypes   |                                    |                                              |                                              |                                                     |         |
| Dystonia-parkinsonism    | 0                                  | 3 (60.0%)                                     | 9 (52.9%)                                     | 2 (25.0%)                                           | 0.07    |
| Early-onset PD           | 5 (100.0%)                        | 0                                             | 6 (35.3%)                                     | 6 (75.0%)                                           | 0.01*   |
| HSP                      | 0                                  | 1 (20.0%)                                     | 2 (11.8%)                                     | 0                                                   | 0.78    |
| Ataxia                   | 0                                  | 1 (20.0%)                                     | 0                                             | 0                                                   | 0.68    |

Data are the number (%) or the mean ± SD. PLAN, Phospholipase A2 group VI-associated neurodegeneration; PD, Parkinson’s disease; HSP, hereditary spastic paraparesis. **P < 0.05; ***P < 0.01. P-values that compare individual characteristics between four groups with different genotypes were evaluated with an analysis of variance. Variables without a normal distribution were compared with the Kruskal-Wallis test, the non-parametric equivalent of the independent sample t-test.
levodopa-responsive EOPD (25, 30). Consistent with initial reports, our two patients with this same mutation had comparable phenotypes and there were no signs of iron accumulation in the globus pallidus in brain MRIs. The PLA2G6 gene encodes a group of VIA calcium-independent phospholipase A2 (iPLA2β) enzymes, which participate in various cellular functions, including phospholipid metabolism, membrane homeostasis, calcium signaling, apoptosis, and mitochondrial function. Thus, these functions could be perturbed by PLA2G6 gene mutations [24]. A homozygous c.991G > T (p.D331Y) knock-in mouse model exhibited dopaminergic neuron degeneration in the substantia nigra, caused by mitochondrial dysfunction, elevated endoplasmic reticulum stress, and transcriptional abnormalities, conforming its pathogenicity in neuronal degeneration [24]. A previous in vitro study showed that patients with the homozygous c.991G > T (p.D331Y) mutation had 30% enzymatic activity remaining in the PLA2G6 protein by using the modified kit originally designed for cytosolic Ca2+-dependent PLA2 (cPLA2) (cPLA2 Assay Kit, Cayman Chemicals) in HEK293 T cells transfected with human mutant constructs (25). An incomplete loss of the iPLA2β enzyme could partially explain the relatively milder clinical and neuroimaging phenotypes of patients with homozygous c.991G > T (p.D331Y) mutations, compared to patients with other mutations in PLA2G6.

The crystal structure of iPLA2β is complex, and the different mutation sites are disparately located on the enzyme [1]. Different mutation sites in the different domains of iPLA2β can lead to different changes in enzymatic activities; however, iPLA2β enzyme activity is the crucial factor that affects the clinical phenotypes of PLAN [33]. For example, the activity of iPLA2β was reduced by 70%, with some remaining enzymatic activity, in cells that expressed p.D331Y, compared to wild-type cells [6]; in contrast, iPLA2β with the p.H597fx69 frameshift mutation exhibited less than 6% enzyme activity compared to the wild-type iPLA2β [34]. The compound heterozygous genotype of p.D331Y and p.M358IfsX mutations was first reported in a Chinese patient that presented with dystonia-parkinsonism [8]. Our first index patient with these same mutations shared similar clinical manifestations, including early age at onset, prominent dystonia, depression, and cognitive decline. The MRI scans in both patients did not show signs of iron accumulations in globus pallidus. The c.1077G > A (p.M358IfsX) mutation, which is located at the splicing junction, resulted in c.1074_1077del.GTCG, and caused aberrant RNA splicing, which resulted in a frame-shift mutation. We hypothesized that this frame-shift mutation might perturb iPLA2β enzyme activity. Indeed, patients with homozygous p.D331Y mutations often presented with levodopa-responsive EOPD, but patients with compound heterozygous p.D331Y and p.M358IfsX mutations often presented with dystonia-parkinsonism, with features of dystonia, pyramidal signs, ataxia, and psychiatric comorbidities. Accordingly, we speculated that iPLA2β enzyme activity might be less in neurons that expressed the p.M358IfsX mutation than in neurons that expressed the p.D331Y mutation. Further functional studies are needed to clarify the molecular mechanism that leads to the clinical heterogeneity associated with different mutations in PLA2G6.

In addition to levodopa-responsive EOPD and dystonia-parkinsonism, 3 patients (from the literature review) having PLA2G6 mutations and displayed HSP, which findings extended our current understanding of the spectrum of clinical phenotypes associated with adult-onset PLAN. Moreover, one patient had compound heterozygous c.991G > T (D331Y) and c.1648delC mutations and presented with prominent ataxia, pyramidal signs, and depression, but did not show signs of parkinsonism or dystonia [10]. That presentation was also rare in adult-onset PLAN. In addition to diverse motor symptoms, neuropsychiatric symptoms comprise one of the main features of adult-onset PLAN. Our index patient with compound heterozygous p.D331Y and p.M358IfsX mutations had severe depression, and one of the two patients with a homozygous p.D331Y mutation also had depression and prominent psychotic symptoms. Many reports also found neuropsychiatric symptoms or behavioral changes in the initial presentations of patients with PLA2G6 mutations [3, 12, 13, 18, 23, 25, 27]. Early cognitive decline or psychiatric symptoms with motor symptoms, such as parkinsonism or dystonia, should prompt clinicians to include PLAN in their differential diagnoses. In those cases, genetic testing for PLA2G6 mutations are warranted, even when brain MRIs show no iron accumulation in the globus pallidus. Moreover, due to the susceptibility to developing psychotic symptoms, dopaminergic agents for treating parkinsonism symptoms in these patients should be carefully titrated and closely monitored to identify psychiatric complications during treatment.

This study had some limitations. First, due to the rarity of the disease, the number of cases was limited. This limitation might have attenuated the statistical power of the results in the comparison of clinical phenotypes among different PLA2G6 mutations. Moreover, due to the diverse clinical manifestations, including motor and neuropsychiatric involvements, the clinical assessments might not have been comprehensive, in every case, in the literature review. Furthermore, although our study focused on adult-onset PLAN, some family members of the index patient may have symptoms since the childhood and we still enrolled these patients into the analysis to have a better understanding of the clinical presentation of the same mutation within the family. Future studies should include thorough clinical, functional
imaging, and genetic analyses, with a long-term follow-up, to provide a better understanding of the correlations between genotype and phenotype in PLAN.

In summary, our findings suggested that adult-onset PLAN could present with purely early-onset levodopa-responsive parkinsonism features, with no brain iron accumulation, particularly in patients with homozygous c.991G > T (p.D331Y) mutations. The homozygous c.991G > T (p.D331Y) mutations were exclusively found in patients of Chinese ethnicity, suggesting a common founder effect. Patients with compound heterozygous mutations had heterogeneous phenotypes, including dystonia-parkinsonism, HSP, and ataxia, and these were often combined with diverse neuropsychiatric symptoms. The wide intra- and inter-familial phenotypic variability of adult-onset PLAN may contribute from other environmental and/or genetic modifiers that might probably modulate the disease presentation. Future studies encompassing whole genome sequencing in patients with PLAN are needed to delineate the potential modifier genes of this disease.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s12883-020-01684-6.

**Abbreviations**

PLA2G6: Phospholipase A2 group VI; PLAN: Phospholipase A2 group VI (PLA2G6) mutations associated with neurodegeneration

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**Authors’ contributions**

Study concept and design: CH. Acquisition of data: YT, HY, PL and CH. Analysis and interpretation of data: YT and CH. Drafting of the manuscript: YT. Critical revision of the manuscript for important intellectual content: CH. Study supervision: CH. All authors have read and approved the final version of the manuscript.

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**Availability of data and materials**

All the relevant raw data in the current study will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

**Ethics approval and consent to participate**

This study was approved by the institutional review board of National Taiwan University Hospital and all study participants gave their informed consents before entering the study. Our study is in accordance with the Declaration of Helsinki and CARE guidelines/methodology. All authors agreed the Publish Statements of BMC Neurology.

**Consent for publication**

Written consent for publication was obtained from each of the participants in this study.

**Competing interests**

All authors have no competing interests or conflicts of interest.

Chin-Hsien Lin is a member of the editorial board (Associate Editor) of this journal.

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