Case Report

CAPN1 Variants as Cause of Hereditary Spastic Paraplegia Type 76

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1. Background

Hereditary spastic paraplegias (HSP) are a group of heterogeneous degenerative disorders characterized by lower limb spasticity and weakness due to progressive degeneration of corticospinal tracts [1]. HSP can present as a pure form only with pyramidal symptoms, or as a complex form associated with other symptoms. HSP are transmitted in all modes of inheritance [2]. The autosomal dominant mode of inheritance is the most prevalent representing 70% of cases. Mutation in SPAST gene accounts for 40% of the autosomal dominant HSP. In the recessive HSP, the most frequent mutation is in SPGII. We report a case of autosomal recessive spastic paraplegia type 76 (SPG76, OMIM #616907) due to heterozygous variants of CAPN1 in an Argentinean subject.

2. Case Presentation

A 38-year-old Argentinean female presented with slowly progressive unsteadiness noticed first at age 23. She reported pronounced instability and gait problems as disease progressed. Her gait problems were described as short steps, with starting hesitation, fear of falling, and needing to hold from walls to avoid falling. She also reported several falls, dizziness, neck pain, and constipation. Symptoms progressed over the years affecting her mobility and functionality. She currently needs assistance for moving around. No relevant medical, family, or psychosocial history was reported. No past interventions were reported.

On neurological examination (Video 1), she presented dysarthria, interrupted slow horizontal and vertical eye movements, and slow horizontal saccades. She manifested spasticity and hyperreflexia more pronounced in her lower extremities. Mild cervical dystonia with bradykinesia was also observed. She showed ataxic symptoms more pronounced on her left upper extremity. Gait was spastic and no cognitive abnormalities were observed.

Brain MRI with and without contrast was unremarkable. Whole-exome sequencing analysis identified two heterozygous variants in CAPN1. Conclusions. Clinicians should screen for CAPN1 mutation in a young female patient without significant family history with a spastic paraplegia syndrome associated with other symptoms.
| Ethnicity       | Age at onset | Age at diagnosis | Gender | Lower limbs spasticity | Upper limbs spasticity | Ataxia | Dysarthria | Oculomotor Impairment | Exon or Intron affected | Mutation | Type              | Heterozygous / Homozygous | Consanguinity | Brain MRI | NCS and SSEP |
|----------------|--------------|------------------|--------|------------------------|------------------------|--------|------------|----------------------|------------------------|-----------|-------------------|-----------------------------|----------------|-----------|-------------|
| Latin American | NA           | NA               | NA     | +                      | +                      | -      | -          | -                    | -                     | c.1176G>A   | p.Thr392 Stop gain mutation | Homozygous                  | +             | NA         | NA          |
| Latin American | NA           | NA               | NA     | +                      | +                      | -      | -          | -                    | -                     | c.1176G>A   | p.Thr392 Stop gain mutation | Homozygous                  | +             | NA         | NA          |
| Latin American | NA           | NA               | NA     | +                      | +                      | -      | -          | -                    | -                     | c.1176G>A   | p.Thr392 Stop gain mutation | Homozygous                  | +             | NA         | NA          |
| Latin American | 22           | 37               | F      | +                      | +                      | -      | -          | -                    | -                     | c.1176G>A   | p.Thr392 Stop gain mutation | Homozygous                  | -             | NA         | NA          |
| Caucasian      | 20           | 46               | F      | +                      | +                      | -      | -          | -                    | -                     | c.675C>A    | p.Tyr225 Novel LoF Mutation | Homozygous                  | -             | NA         | NA          |
| Caucasian      | 30           | 51               | M      | +                      | +                      | +      | -          | -                    | -                     | c.675C>A    | p.Tyr225 Novel LoF Mutation | Homozygous                  | -             | NA         | NA          |
| Latin American | 30           | 42               | F      | +                      | +                      | +      | -          | -                    | -                     | c.675C>A    | p.Tyr225 Novel LoF Mutation | Homozygous                  | +             | NA         | NA          |
| Latin American | 38           | -                | M      | +                      | +                      | +      | -          | -                    | -                     | c.1176G>A   | p.Thr392 Stop gain mutation | Homozygous                  | +             | NA         | NA          |
| Arab           | 20           | 31               | F      | +                      | +                      | -      | +          | -                    | Ex:8                   | c.884G>C    | p.Arg295 Pro Novel LoF Mutation | Homozygous                  | +             | NA         | Normal       |
| Arab           | NA           | NA               | NA     | NA                     | NA                     | NA     | NA         | NA                   | Ex:8                   | c.884G>C    | p.Arg295 Pro Novel LoF Mutation | Homozygous                  | +             | NA         | NA          |
| Arab           | NA           | NA               | NA     | NA                     | NA                     | NA     | NA         | NA                   | Ex:8                   | c.884G>C    | p.Arg295 Pro Novel LoF Mutation | Homozygous                  | +             | NA         | NA          |
| Arab           | 35           | 47               | M      | +                      | +                      | -      | +          | -                    | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | Moderate Sensory Axonal Neuropathy |
| Arab           | 36           | 44               | F      | +                      | +                      | +      | +          | +                    | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | NA            | NA         | Moderate Sensory Axonal Neuropathy |
| Arab           | 22           | 42               | M      | +                      | +                      | -      | +          | -                    | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | Normal       |
| Arab           | 39           | 40               | M      | +                      | +                      | +      | +          | -                    | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | NA          |
| Arab           | NA           | NA               | NA     | NA                     | NA                     | NA     | NA         | NA                   | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | NA          |
| Arab           | NA           | NA               | NA     | NA                     | NA                     | NA     | NA         | NA                   | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | NA          |
| Arab           | NA           | NA               | NA     | NA                     | NA                     | NA     | NA         | NA                   | Ex:4                   | c.1176G>T   | p.Glu392 Stop variant          | Homozygous                  | +             | NA         | NA          |
| Caucasian      | 24           | 30               | F      | +                      | -                      | -      | -          | -                    | -                     | c.460delC   | p.Phe154Argfs Deletion            | Heterozygous                | -             | NA         | Normal       |
| Ethnicity | Age at onset | Age at diagnosis | Gender | Lower limbs spasticity | Upper limbs spasticity | Ataxia | Dysarthria | Oculomotor Impairment | Mutation Type | Exon or Intron | Brain MRI | NCS and SSEP |
|-----------|-------------|------------------|--------|------------------------|-----------------------|--------|-----------|------------------------|---------------|---------------|-----------|--------------|
| Caucasian | 35          | 35               | M      | +                      | -                     |        | -         | -                      | Ex:4          | p.Pro136Argfs*40 | NA        | Normal       |
| Indian    | 39          | 43               | F      | +                      | +                     | +      | +         | +                      | Ex:3          | c.406delC   | NA        | Normal       |
| Indian    | 29          | 39               | F      | +                      | +                     | +      | +         | +                      | Ex:4          | c.1605+5G>A  | NA        | Normal       |
| Indian    | NA          | NA               | F      | NA                     | NA                    | NA     | NA        | NA                     | NA            | NA            | NA        | NA           |
| Caucasian | 21          | 19               | F      | +                      | +                     | +      | +         | +                      | Ex:6          | c.759+1G>A  | NA        | Normal       |
| Arab      | 22          | 37               | F      | +                      | +                     | +      | +         | +                      | Ex:10         | c.1176G>A   | NA        | Normal       |
| Arab      | 15          | 30               | F      | +                      | +                     | +      | +         | +                      | Ex:10         | c.1176G>A   | NA        | Normal       |
| Asian     | 37          | 37               | M      | +                      | +                     | +      | +         | +                      | Ex:12         | c.1353+2T>C  | NA        | Normal       |
| Latin American | 23 | 23 | M | + | + | + | + | + | Ex:12 and 16 | c.1729+1G>A | c.1353+2T>C | Normal | Normal |

**Abbreviations:** F: female, M: male, +: present, -: absent, LoF: loss of function, DYSF: dysferlin, MRI: magnetic resonance image, C: cerebral, S: spinal, NCS: nerve conduction studies, SSEP: somatosensory evoked potentials, NA: not available.
access, we decided to optimize our resources studying the patient using whole-exome sequencing (CentoDX™, Centogene AG, Germany). The analysis identified two variants in CAPN1 (MIM:114220) considered as probably pathogenic Class 2, according to the American College of Medical Genetics and Genomics criteria. She was heterozygous for a splicing mutation in intron 16 (c.1729+1G>A) and a second splicing mutation in intron 12 (c.1353+2T>C). Carrier testing in the parents was not performed. Due to the strong phenotypic overlap between the symptoms and previously reported cases, we consider the detected variants as pathogenic of SPG76.

3. Discussion

We report two pathogenic variants of CAPN1 gene and the first case affecting two noncoding regions (introns) in a Latin-American patient. Table 1 describes all SPG76 reported cases in the literature [3, 4]. We observed that female patients are more commonly (67%) affected, with a mean age of onset of 19.8 years (Min. = 5, Max. = 39), most had family history of consanguinity (71%), and most were homozygous (77%). All initiated with lower limb spasticity, 85% reported upper limb spasticity, 58% showed ataxia, and 41% reported dysarthria. Our case also presented with oculomotor abnormalities. Three cases showed cerebellar atrophy and 1 spinal atrophy on MRI.

In comparison with other published cases, we found similarities in that all of them presented lower limb spasticity and ataxia. The difference from our case was the oculomotor abnormalities, which was also reported in only one other case [5]. We suggest that the combined phenotype of spasticity and ataxia with oculomotor abnormalities, in a young female patient of Arab origin, could be a diagnostic clue for SPG76. The age of onset of our case was similar to that previously reported. All of the subjects experienced pronounced instability and gait problems as disease progresses [6].

CAPN1 mutations account for 2.2% of autosomal recessive HSP. CAPN1 is located in chromosome 11q13 and encodes calpain 1, a calcium-activated cysteine protease that is widely present in the central nervous system. The exact role of calpain 1 in humans is unclear; however, studies in animal models suggest that calpain 1 is involved in synaptic plasticity, neuronal migration, neuronal necrosis, and maintenance [7].

4. Conclusions

Our report adds to the clinical and genetical spectrum of CAPN1-related SPG76 disorders. We recommend clinicians to consider screening for CAPN1 in a young female patient with spastic paraplegia with additional neurological symptoms without significant family history.

**Data Availability**

All data generated or analyzed during the case report are included in the published article.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images or videos.

**Conflicts of Interest**

The authors report no financial or nonfinancial conflicts of interest.

**Authors’ Contributions**

Daniel Martinez-Ramirez and Jesus Eduardo Garcia-Berlanga were responsible for conception, organization, and execution. All the authors were responsible for the preparation of the manuscript: writing of the first draft, review and critique, and reading and approving the final version of the manuscript.

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We would like to thank the patient for authorizing us to use her clinical data to make it available for the medical community.

**Supplementary Materials**

Video Legends: We can observe interrupted slow horizontal and vertical eye movements with slow horizontal saccades. She had spasticity and hyperreflexia more pronounced in lower extremities. She also showed bilateral Hoffman and Trömmer signs, with clonus in lower extremities, and presence of Babinski sign bilaterally. She presented cervical dystonia with laterocollis to the left, and mild bradykinesia was observed during rapid movements. Finger to nose test showed dyssynergia and hypometric movements, rapid alternating movements with dysdiadochokinesia, past pointing, and finger chasing with dyssynergia and dysmetria more pronounced on left upper extremity. Gait was spastic type with scissoring legs. (Supplementary Materials)

**References**

[1] C. Blackstone, “Hereditary spastic paraplegia,” *Handbook of Clinical Neurology*, vol. 148, pp. 633–652, 2018.

[2] J. Finsterer, W. Löscher, S. Quasthoff, J. Wanschitz, M. Auer-Grumbach, and G. Stevanin, “Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance,” *Journal of the Neurological Sciences*, vol. 318, no. 1-2, pp. 1–18, 2012.

[3] J. Lambe, B. Monaghan, T. Munteanu, and J. Redmond, “CAPN1 mutations broadening the hereditary spastic paraplegia/spinocerebellar ataxia phenotype,” *Practical Neurology*, vol. 18, no. 5, pp. 369–372, 2018.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| HSP          | Hereditary spastic paraplegia |
| SPAST        | Spastin gene |
| SPG          | Spastic paraplegia gene |
| CAPN1        | Calpain 1 gene |
| MRI          | Magnetic resonance imaging |
[4] C. Kocoglu, A. Gundogdu, G. Kocaman et al., “Homozygous CAPN1 mutations causing a spastic-ataxia phenotype in 2 families,” Neurology: Genetics, vol. 4, no. 1, p. e218, 2018.

[5] Z. Gan-Or, N. Bouslam, N. Birouk et al., “Mutations in CAPN1 cause autosomal-recessive hereditary spastic paraplegia,” American Journal of Human Genetics, vol. 98, no. 6, p. 1271, 2016.

[6] F. Peng, Y. Sun, C. Quan, J. Wang, and J. Wu, “Two novel homozygous mutations of CAPN1 in Chinese patients with hereditary spastic paraplegia and literatures review,” Orphanet Journal of Rare Diseases, vol. 14, no. 1, p. 83, 2019.

[7] M. Baudry and X. Bi, “Calpain-1 and calpain-2: the yin and yang of synaptic plasticity and neurodegeneration,” Trends in Neurosciences, vol. 39, no. 4, pp. 235–245, 2016.