



## Hereditary spastic paraplegia initially diagnosed as cerebral palsy

Oksana Suchowersky<sup>a,\*</sup>, Setareh Ashtiani<sup>b</sup>, Ping-Yee Billie Au<sup>b</sup>, Scott McLeod<sup>c</sup>,  
Mehrdad A. Estiar<sup>d</sup>, Ziv Gan-Or<sup>d,e</sup>, Guy A. Rouleau<sup>d,e</sup>

<sup>a</sup> University of Alberta, Departments of Medicine (Neurology) and Medical Genetics, Edmonton, Canada

<sup>b</sup> Alberta Children's Hospital, Medical Genetics, Calgary, Canada

<sup>c</sup> Alberta Children's Hospital, Developmental Pediatrics, Calgary, Canada

<sup>d</sup> McGill University, Department of Human Genetics, Montreal, Canada

<sup>e</sup> McGill University, Department of Neurology and Neurosurgery, Montreal, Canada

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### ABSTRACT

**Introduction:** Spastic diplegia presenting in infancy is common to both cerebral palsy (CP) and hereditary spastic paraplegia (HSP). We report the clinical and genetic features of a cohort of Alberta patients with a diagnosis of HSP, who were initially diagnosed with CP.

**Methods:** Fourteen patients with an initial diagnosis of CP were identified from an Alberta registry of HSP patients via chart review. Whole exome sequencing (WES) was performed to identify genetic causes.

**Results:** From 90 families in the database, individuals in 29 families had a pediatric presentation of spasticity, with 20 presenting under 3 years of age. Individuals from 14 families had received an initial diagnosis of CP and correct diagnosis was made after neurogenetic assessment due to symptom progression. All had early onset (<3 years) of symptoms. WES identified pathogenic or likely pathogenic mutations in nine cases involving six genes: *ATL1*, *PLP1*, *PNPLA6*, *SACS*, *SPAST*, and *SYNE1*. In five families, WES did not reveal a genetic etiology but progression of symptoms and positive family history suggests HSP is the most likely diagnosis.

**Conclusion:** In our cohort, 70% of HSP children presenting with spasticity under 3 years had been misdiagnosed with CP. In a young child presenting with spastic diplegia without clear history of prematurity, intrauterine growth restriction, infection or vascular insult, it is important to consider HSP. Accurate diagnosis has implications for prognosis, management, and recurrence risk.

### 1. Introduction

Hereditary spastic paraplegias (HSPs) encompass a group of rare clinically and genetically heterogeneous neurodegenerative disorders. Prevalence is estimated at 1.8 in 100,000 [1]. HSPs begin with spasticity and weakness in the lower limbs, and are categorized as either uncomplicated (pure) or complicated (complex). In the uncomplicated phenotype, neurologic impairment is limited to lower extremity spastic weakness, bladder overactivity, and mild decrease of lower extremity vibration sensation. Upper limb involvement can develop over time. In complicated forms, features such as optic atrophy, ataxia, cognitive impairment, peripheral neuropathy, seizures, and dystonia can occur. Onset ranges from infancy to late adulthood, and is associated with slow progression over decades. Currently, over 76 causative genes have been

identified, inherited as autosomal dominant, recessive or X-linked disorders [2,3].

Cerebral palsy (CP) is the most common motor disorder in childhood, with an estimated prevalence of 2–3.5 per 1000 births [4], resulting in static neurological symptoms due to non-progressive disturbances in the developing brain. Recently, it has been shown that CP can be associated with chromosomal abnormalities and risk factor genes [5,6]. There also is increasing recognition that single gene disorders with onset in infancy may be genetic mimics of CP [7–9].

In 2012, a Canadian-wide registry to collect patients with HSP was undertaken with Alberta being one of the main sites [10]. We present the data with respect to HSP patients in the Alberta cohort were given an initial diagnosis of CP. To our knowledge, no other group has examined the frequency of a previous CP diagnosis in a large cohort of HSP

\* Corresponding author at: Departments of Medicine (Neurology) and Medical Genetics, University of Alberta, 7-112Q Clinical Sciences Building, 11350 83 Ave, Edmonton, Alberta T6G 2G3, Canada.

E-mail address: [suchower@ualberta.ca](mailto:suchower@ualberta.ca) (O. Suchowersky).

<sup>1</sup> ORCID: 0000-0001-6783-4956

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patients in Canada.

## 2. Methods

From 2012 to 2019, patients with clinical suspicion of HSP were recruited through movement disorders, psychiatry, and genetics clinics in Edmonton and Calgary, which draw patients from the province of Alberta. The project was approved by research ethics committees at University of Alberta and University of Calgary. All patients and caregivers gave consent to research participation and publication of results. Demographics, and clinical data was collected through chart review. Clinical assessment and MRI review was performed by one investigator (OS). Collection of detailed family history was done by another investigator (SA).

Patients with cerebellar ataxia in addition to spasticity with abnormalities on clinical testing for autosomal dominant spinocerebellar ataxia repeat expansion disorders (SCAs 1–8, SCA17), Friedreich ataxia (*FXN*), ataxia telangiectasia (*ATM*) or chromosomal microarray (60 K oligonucleotide array) were excluded from enrollment in the study.

MRI brain and spine were completed on all patients. Most individuals had a trial of levodopa, and none showed symptom improvement.

During this time, clinical testing for HSP was not approved for funding, and could only be obtained through research. Extracted DNA from peripheral blood was sent to McGill University for whole exome sequencing (WES) [10]. Whole-exome capture, sequencing and

bioinformatic analysis were performed as previously described [10] and analyzed using a list of 785 genes which had been reported to have spasticity as part of the phenotype. Findings were verified at clinically accredited laboratories. Where required, segregation was done by Sanger sequencing to identify whether variants were de novo, if parents were heterozygous carriers and/or to identify other potentially affected individuals. When clinical funding became available in 2019, individuals where research WES did not identify a mutation had clinical panel testing performed.

## 3. Results

A total of 119 individuals from 90 families were recruited. Analysis of the registry revealed 29 families had a pediatric presentation of spasticity, average age of onset 3.8 years (ranging from < 1 to 14 years). Of those individuals, 14 (48%) had received an initial diagnosis of CP. The average age of onset in this group was 1.7 years (ranging from < 1 to 3 years). In 20 families with HSP with onset under the age of 3, 70% had been misdiagnosed with CP on initial assessment. Onset of spasticity after the age of 3 did not lead to misdiagnosis.

Chart and in-person review of these cases showed that none had significant prenatal or perinatal traumatic events, or MRI findings suggestive of intracranial injury. In addition, 7 had a family history of gait abnormalities. Toe walking and abnormal gait were typical presenting features (Table 1).

**Table 1**  
Characteristics of families with pediatric onset of HSP diagnosed with CP.

Case	Age of Onset (Yrs)	Sex	Symptoms at presentation	Symptoms other than spasticity	Family history	Genetic Results	Inheritance
1	1.5	Male	Spastic diplegia	Intellectual disability	None	<i>SPAST</i> c.1496G > A, p.(Arg499His), pathogenic	Autosomal dominant, <i>de novo</i>
2	1	Female	Spastic diplegia	None	None	<i>SPAST</i> c.1220G > A, p.(SER407Asn), pathogenic	Autosomal dominant, <i>de novo</i>
3	3	Male	Spastic diplegia	None	Father affected	<i>SPAST</i> c.1413 + 3_1413 + 6del, likely pathogenic	Autosomal dominant, paternally inherited
4	2.5	Male	Developmental milestones delayed, spasticity	None	Mother affected	<i>ATL1</i> c.715C > T, p.(Arg239Cys), pathogenic	Autosomal dominant, maternally inherited
5	birth	Male	Developmental milestones delayed, spasticity	Cognitive impairment, dysarthria, slowed eye movements	Brother affected	<i>PLP1</i> c.191 + 1G > A, pathogenic	X-linked, maternally inherited
6	2	Female	Gait problems	Ataxia, peripheral neuropathy	None	<i>SACS</i> c.423_424del, p.(Glu141Aspfs*42) and <i>SACS</i> c.10907G > A, p.(Arg3636Gln), both likely pathogenic, and c.10954C > A, p.(Pro3652Thr), which is of uncertain significance	Autosomal recessive, parents unavailable for testing
7	0.5	Male	Gait problems, toe walking	Ataxia, peripheral neuropathy	None	<i>SACS</i> c.9144delC, p.(Thr3050Glnfs*2) and c.167_171 + 31del, both likely pathogenic	Autosomal recessive, compound heterozygous
8	1	Male	Leg weakness, spasticity,	Ataxia	Brother affected	<i>SYNE1</i> c.17816_17820del, p.(Asp5939Alafs*13)	Autosomal recessive, homozygous
9	2	Male	Toe walking	Motor neuropathy, saccadic smooth pursuit	None	<i>PNPLA6</i> c.3200C > T, p.(Thr1067Met) and c.3350C > T, p.(Thr1117Met), both likely pathogenic	Autosomal recessive, compound heterozygous
10	3	Male	Spastic diplegia	None	None	unsolved	N/A
11	2	Female	Spastic diplegia	None	Two brothers affected	unsolved	N/A
12	2	Female	Spastic diplegia	Cognitive impairment	Mother affected	unsolved	N/A
13	birth	Male	Gait problems	Cognitive impairment, nystagmus, optic nerve atrophy	None	unsolved	N/A
14	0.5	Male	Developmental milestones delayed, spasticity	Cognitive impairment, peripheral neuropathy	Brother affected	unsolved	N/A

Of the 14 cases, 4 were consistent with pure HSP, and nine with complex (Table 1). Microarray testing was normal. MRI brain and cervical spine were normal, except for case 8, where cerebellar atrophy was identified.

WES identified pathogenic or likely pathogenic mutations in nine of the 14 families (64%): one *ATL1* (SPG3A, autosomal dominant, inherited), one *PLP1* (SPG2, X-linked), one *PNPLA6* (SPG39, autosomal recessive), three *SPAST* (SPG4, autosomal dominant, one inherited and two *de novo*); two *SACS* (ARSACS, autosomal recessive, compound heterozygous), and one *SYNE1* (SCAR8, autosomal recessive, homozygous mutation). In five families, WES and clinical panel testing did not reveal an underlying genetic etiology. However, due to symptom progression, lack of history of pre or perinatal injury, normal MRI, as well as positive family history, HSP remains the most likely diagnosis.

With identification of a genetic abnormality in one individual, other family members could be identified who had been misdiagnosed as having CP, as in case 4 (Table 1). This five-year-old boy presented with lower extremity weakness in infancy. He was born to a 28-year-old, G1, P0 at full-term by an elective C-section due to the mother's spastic diplegia. Apgar's were normal. Based on motor delays, he had been diagnosed with CP by a pediatrician. The mother reported that she had motor delay from infancy, and had also been given a diagnosis of CP, with counseling that this was "not genetic". On exam, both mother and son had similar findings with slowly progressive upper motor signs in the legs. Genetic testing revealed a heterozygous *ATL1* c.715C > T, p.(Arg239Cys) pathogenic variant in both, consistent with autosomal dominant spastic paraplegia (SPG3A, MIM #182600). Given the otherwise negative family history, this initially appeared to be a *de novo* mutation in the mother, but further testing showed the maternal grandmother to be a mosaic for the mutation.

#### 4. Discussion

CP has historically been used as a term to describe static motor encephalopathy, with motor impairment due to prenatal or perinatal brain injury. Diagnosis was based on clinical history, exam and brain imaging. It is now recognized that some individuals who have CP or CP-like presentation have an underlying genetic etiology.

10–20% of individuals who fulfill criteria for CP may have chromosomal abnormalities, such as copy number variants, similar to that seen in autism spectrum disorder [5,11]. A number of susceptibility genes have also been described [6]. Equally significant is data from large scale exome sequencing studies of identification of single gene abnormalities as "genetic mimics" for CP including HSPs, benign hereditary chorea, dopa responsive dystonia, and metabolic disorders [8–10]. The yield may be as high as 32.7% in pediatric patients, and 10.5% in adult patients [11].

Spastic diplegia presenting in infancy is a presentation common to both CP and HSP [12]. Our review of HSP patients in Alberta identified that 70% of patients presenting with leg spasticity and/or gait abnormalities under the age of 3, had received an initial diagnosis of CP in spite of no evidence of prenatal or perinatal injury, and even in the presence of a positive family history. 64% of these had genetic confirmation of an HSP diagnosis, which is higher than previous reports [8,11]. This is likely related to the tight criteria for patient selection.

Factors contributing to incorrect diagnosis included the absence or incomplete ascertainment of family history. In our cohort, having an affected parent did not prompt early diagnosis and it was the parents with similar symptoms who recognized the possibility of a genetic cause, and requested a referral for genetic assessment. It is also important to note that true absence of family history does not rule out a genetic condition due to *de novo* mutations, and/or mosaicism in a parent.

Secondly, there continues to be lack of awareness that autosomal dominant forms of HSP, such as *SPAST*, can have onset in infancy as well as adulthood [12]. In some cases of HSP, minimal or slow progression further contributes to misdiagnosis [2,12].

CP is a description of a phenomenology and not an etiology. The cases presented in our cohort were initially misdiagnosed with CP and highlight a missed opportunity for an accurate diagnosis. Identification of an underlying genetic disorder is crucial for management of symptoms, health surveillance, prognosis and targeted therapy. A genetic diagnosis has significant impact on the family, with genetic counseling and determination of recurrence in future children.

If desired by the families, keeping these patients in the CP cohort in order to maintain access to specialized care and programs may be appropriate. However, our experience has been that families preferred to have the child's diagnosis updated to HSP.

The study limitations are related to recruitment as only cases which were referred for neurogenetic assessment due to symptom progression were analyzed. For families who may not have access to appropriate specialists, a referral may not have been initiated.

In conclusion, HSP and CP can both present with spastic diplegia in infancy. Careful clinical assessment, looking for unexpected phenotypes and symptom progression, and detailed review of the family history to differentiate between the two conditions is recommended. Genetic testing including microarray, appropriate gene panels or WES is now available for accurate diagnosis, even in sporadic cases. Correct diagnosis has significant impact on prognosis, treatment and counseling of recurrence risks.

#### CRedit authorship contribution statement

**Oksana Suchowersky:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Writing – original draft. **Setareh Ashtiani:** Data curation, Formal analysis, Investigation, Writing – original draft. **Ping-Yee Billie Au:** Formal analysis, Investigation, Writing – review & editing. **Scott McLeod:** Investigation, Writing – review & editing. **Mehrdad A. Estiar:** Formal analysis, Data curation. **Ziv Gan-Or:** Funding acquisition, Investigation, Methodology, Writing – review & editing. **Guy A. Rouleau:** Funding acquisition, Investigation, Methodology, Writing – review & editing.

#### Declaration of Competing Interest

O. Suchowersky reports no disclosures relevant to the manuscript. S. Ashtiani reports no disclosures relevant to the manuscript. P.Y.B. Au reports no disclosures relevant to the manuscript. S. McLeod reports no disclosures relevant to the manuscript. M. A. Estiar reports no disclosures relevant to the manuscript. Z. Gan-Or reports no disclosures relevant to the manuscript.

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