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Parkinsonism and Related Disorders

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Spinocerebellar ataxias type 3 and 10: Onset and progression of ataxia during pregnancy and puerperium

Keywords:

Cerebellar ataxia
Pregnancy
Puerperium
Spinocerebellar ataxias
SCA3
SCA10

SCA3 is characterized by gait ataxia, dysarthria and nystagmus. It is caused by mutations in the *ATXN3/DMJ* gene (OMIM#607047), which when mutated has an increased number of CAG repeats. SCA10, a rarer subtype, is characterized by ataxia with cerebellar atrophy and, in some case, seizures; dysarthria and dysphagia are common as the disease progresses. SCA10 is caused by expansion of ATTCT pentanucleotide repeats in the *ATXN10* gene (OMIM#611150).

Previous clinical observations showed that genetically determined neurodegenerative conditions – such as SCA10 and chorea-acanthocytosis – may be influenced by hormonal changes. In the same context, basic research studies showed that several hormone receptors are expressed in the cerebellum (including receptors for estrogen and progesterone), and that cerebellar function is strongly influenced by hormonal factors [1–4].

Based on the above-mentioned observations, we conducted a retrospective study to assess whether pregnancy and puerperium contribute to development and/or worsening of ataxia in women with SCA3 and SCA10.

We included pregnant women with genetically confirmed SCA3 ($n = 22$) or SCA10 ($n = 18$) who were being regularly followed at our institution (Hospital de Clínicas/UFPR). Demographic and clinical variables included age, age of onset, change in ataxia during pregnancy/puerperium, and baseline assessment of ataxia severity using the Brazilian validated Scale for the Assessment and Rating of Ataxia (SARA) [5]. Scores for the SARA range from zero (no ataxia) to 40 (severe ataxia). This study was approved by our institution's ethics committee; all participants signed informed consents.

Demographic and clinical data as well as results are shown in Table 1. Twelve patients with SCA10 ($n = 12/18$, 66.7%) and one patients with SCA3 ($n = 1/22$, 4.5%) reported either new onset or worsening ataxia during pregnancy (third trimester) or puerperium (within seven days of delivery) ($p < 0.0001$). Among the 12 patients with SCA10 who experienced new onset/worsening ataxia during pregnancy/puerperium, nine ($n = 9/12$, 75%) had new onset ataxia whereas three ($n = 3/12$, 25%) had worsening ataxia. The

latter had a mean SARA of 8 prior to pregnancy and 12 during pregnancy/puerperium. The only patient with SCA3 who experienced new onset/worsening ataxia during pregnancy or puerperium actually developed new onset during pregnancy (third trimester). Importantly, none of the patients included in this study used alcohol or illicit drugs in the perigestational period.

This study presents a possible link between development or worsening of ataxia in patients SCA10 during pregnancy and puerperium as two-thirds of patients with SCA10 included in this study experienced either development or worsening of ataxia during the third trimester of pregnancy or recent puerperium (within 7 days of delivery). Notably, this relationship was not seen in patients with SCA3. We hypothesize that this relationship may be secondary to hormonal changes – estrogen and progesterone – during pregnancy/puerperium.

New onset cerebellar ataxia in patients with SCA10 during pregnancy/puerperium had been previously described. One study reported three patients, from the same family with SCA10, who developed new onset ataxia during pregnancy/puerperium; all three patients had their SCA10 diagnosis confirmed by genetic testing. The authors hypothesized that hormonal changes could have contributed to the development of symptoms [3]. Another study described new onset gait ataxia and dysarthria following pulse therapy with methylprednisolone (for the treatment of immune thrombocytopenic purpura) in a 34-year-old Brazilian woman. Her brain MRI showed cerebellar atrophy, and her family history was positive for SCA10 (aunt and two cousins). Interestingly, the affected relatives also developed ataxia during pregnancy/puerperium [4]. Hormonal changes have also been thought to influence other genetically determined neurodegenerative disorders as per previous description of catamenial and oral contraceptive-induced exacerbation of chorea in chorea-acanthocytosis.

The relationship between cerebellar ataxia and hormonal changes is not fully understood. Basic research studies have identified gonadal steroids receptors in several brain regions, including the cerebellum. Furthermore, steroids synthesized *de novo* in the brain – neurosteroids – appear to modulate both gamma-aminobutyric acid receptors-A (GABA-A) and neurotransmitters in the central nervous system. Additional research focusing on hormonal regulation of cerebellar development and plasticity confirmed that a significant amount of hormone receptors are expressed in the cerebellum and that cerebellar function is influenced by hormonal status [1,2].

An alternative hypothesis as to why women with SCA10 develop new onset or worsening ataxia during pregnancy/puerperium would be that these patients are under great amount of stress [3].

<https://doi.org/10.1016/j.parkreldis.2018.03.025>

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Table 1
Spinocerebellar types 3 and 10 – demographic and clinical data.

	SCA3	SCA10	<i>p</i> *
Number of patients (n)	22	18	
Mean age (SD)	39.4 years (8.4)	38.2 years (8.3)	0.257
Mean age of ataxia onset (SD)	33.1 years (6.1)	30.2 years (4.1)	0.832
Mean number of pregnancies (SD)	2.42 (1.17)	3.57 (1.49)	
Mean SARA score (SD)	9.8 (8.7)	10.4 (5.4)	0.443
Mean repeat expansions (SD) (CAG and ATTCT)	74 \ddagger (3.8)	1900.2 (523.6)	
New onset or worsening of symptoms during pregnancy/puerperium	1 (4.5%)	12 (66.7%)	<0.0001
New onset symptoms during pregnancy/puerperium	1	9	0.002
Clinical worsening during pregnancy/puerperium	0	3	0.083

SCA, spinocerebellar ataxia; SD, standard deviation; SARA, scale for the assessment and rating of ataxia.

*Fisher's exact test; \ddagger available for 16 patients (n = 16/22).

However, this explanation would be less likely because patients with SCA3 did not experience new onset/worsening of symptoms during pregnancy/puerperium. Lastly, it is unclear why the relationship between development or worsening ataxia during pregnancy/puerperium was observed in patients with SCA10 and not SCA3. We hypothesize that patients with SCA10 may have particular abnormalities in the cerebellum and its afferent/efferent connections in the realm of hormonal receptors (gonadal steroids); such abnormalities would not be the same in patients with SCA3.

The main limitation of our study include the possible suboptimal accuracy of retrospective, self-reported data used as main outcome, with no clinical confirmation to corroborate either onset or worsening of symptoms.

The recognition of this intriguing influence of pregnancy/puerperium in the onset and/or aggravation of motor symptoms in SCA10 may have important clinical and pathophysiological implications in SCA10 and other forms of ataxia. Larger studies in SCA and other forms of hereditary degenerative disorders are needed to confirm and expand our preliminary findings.

Author contributions

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Study concept and design; acquisition of data; data analysis and interpretation; drafting manuscript; accepts responsibility for conduct of research.

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Study funding

None.

Disclosure

All authors report no relevant disclosures.

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4 December 2017