A FEMALE CASE OF SPINOCEREBELLAR ATAXIA TYPE 10 WITH SUICIDAL BEHAVIOR AND ENDOCRINPATHIES ASSOCIATED WITH A MASSIVE EXPANSION (ATTCT) OF THE GENE *ATXN10*

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To the editor

Spinocerebellar ataxia type 10 (SCA10) is characterized by ataxia, psychiatric disorders convulsions, and locus at 22q13.311. It is caused by expansions between 800-4500 pentanucleotide ATTCT repeats in intron 9 of the ATXN10 gene[1-2]. The ATXN10 gene encodes ataxin-10 protein (known as E46L) involved in neuritogenesis 1. SCA10 has a founder origin in Mexican, Brazilian, Argentine populattons but is rare in others[3-5]. Within the most frequent psychiatric characteristics are fatigue, severe depression, anxiety and apathy[6-8.] Other non-motor alterations with a psychiatric background as cold intolerance, diaphoresis, nicturia, anorexy and orthostatic hypotension[6-8]. Convulsive crisis are associated to ATTCT expansions higher than 800 repeats[8-9]. There is no association with SCA10 and endocrine disorders. E46L participates in thyroid morphogenesis as well as oncogenesis of prolactinomas through interactions with signaling proteins such as GNB2, ABCE1, CDk12, CDKN3 (UniProt KB-Q90BB4). We describe an atypical clinical case of SCA10 with suicide behavior, psychiatric disorders and endocrinopathies.

CASE REPORT

The proposita aged 20 years-old (table 1), age of onset 12 years with atonic, epileptiform and generalized crisis, later tonic-clonic with a frequency of 10 per year, which had no response to a combined pharmacological treatment (magnesium valproate, lamotrigine, carbamazepine, topiramate, diazepam). Since 8 years-old she presented behavior cane with suicide attempts repeatedly, associated to a major depressive disorder and cognitive disturbances related with despair, irritability, and anxiety as well as aggressiveness which were treated with risperidone 2 mg each 8 hours. The father died of known cause, the mother refers that the proposita presented epilepsy since birth, attacks of anger and anxiety. It is unknown if there are other relatives similarly affected by the paternal line.

The proposita also showed amenorrhea-galactorrhea and congenital hypothyroidism, which currently been treated with bromocriptine (7.5 mg/12 hours) and levotiroxine (100mcg per day). At physical examination showed slow ocular saccades, irritability, aggressiveness, moderate cognitive impairment, hypertropic dysmetria of all limbs, movement disorder and bilateral dysdiadochokinesia, myotatic reflexes ++, fine tremor only in hands, lack of control in movements, unable to use the spoon, right extensor plantar response, gait ataxia, axial and limb stiffness of right predominance, inability to perform everyday tasks, akinetic parkinsonism, and irregular periods and heavy bleeding. It was not possible to explore MFIS, HAMA, DBI scales due to lack of cooperation from the patient. The brain MRI scans revealed moderate cerebellar atrophy and cerebral hemispheres, brainstem, nucleus and lateral raphe, as well as vermix atrophy, which has been progressive with enlargement of the fourth ventricle (figure 1). The pelvic ultrasonogram (PUSG) showed uterus 8, 1x3, 2x6 mm, normal size and shape ovaries, no follicular development. Laboratory exams; Prolactine 50.5-64.9 ng/ml, TSH 11.1 ng/ml (increased) and T4 1.04 ng/ml, LH 3.9 ng/ml, FSH 2.52 ng/ml, Progesterone 0.26, Estradiol 45.2. Prolactine 64.9 (high levels).

Molecular studies. The DNA was extracted from 5 ml of peripheral blood leukocytes of the proposita and her

Table 1 **Comparative clinical features of the *proposita* with other cases**

Clínical features	OMIM	Index	Matsuura T y col. 2000 n=17	Rasmussen y col. 2001, Mexicanos n=18	Grewal RP y col. 2002, Sur de California n=22	Teive HA y col. 2004, Brasileños n=28	Teive HA y col. 2004, Mexicanos n=1	Almeida T y col. 2009, n=14	Teive HA y col. 2010, Mexicanos n=19	Teive HA y col. 2010, Brasileños, n=80	Teive HA y col. 2010 Argentinos, n=5	Teive HA y col. 2010 Venezolanos, n=6	Nascimento FA y col 2019, Sur de Brasil, n=84
Cognitive damage	(+)	(+)	NP	100%	(-)	(-)	(-)	NP	5.3%	(-)	(-)	(-)	3.60%
Depression	(+)	(+)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Behavior disturbances	NA	(+)		100%	18.00%	(-)	(-)		(-)	(-)	(-)	(-)	(-)
Nistagmus	(+)	NV	NP	NP	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	86.00%
Other abnormalities of the ocular movement	(+)	(+)	NP	100%	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Slow saccades	NA	(+)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	7.60%
Vision loss	NA	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	4.80%
Ophthalmoplegia	NA	NV	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	10.81%
Dysphagia	NA	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	7.00%
Urinary urgency	(+)	(-)	NP	NP	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Urinary incontinence	(+)	(-)	NP	NP	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	1.20%
Progressive cerebellar ataxia	(+)	(+)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	(-)
Tremor	NA	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	6.00%
Hipo/arreflexia	NA	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	2.40%
Parkinsonisme	NA	(+)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Ataxic gait	(+)	(+)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	95.20%
Incoordination	(+)	(+)	NP	100%	100%	100%	100%	100%	(-)	100%	100%	100%	(-)
Limb ataxia	(+)	(-)	NP	100%	100%	100%	100%	100%	(-)	100%	100%	100%	(-)
Dysartria	(+)	(-)	NP	100%	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	94.10%
Dysmetría	(+)	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Language troubles	(+)	(+)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	1.20%
Convulsions/ epilepsy	(+)	(+)	NP	100%	2.50%	(-)	3.50%	100%	72.2%	3.75%	100%	80%	4.80%
Pyramidal signs	(+)	(+)	NP	(-)	(-)	(-)	(-)	NP	50%	10%	40%	(-)	2.00%
Hiperreflexia	(+)	(+)	NP	(-)	(-)	(-)	(-)	NP	31.57%	(-)	(-)	(-)	(-)
Dementia	(+)	(-)	NP	(-)	(-)	(-)	(-)	ND	5.3%	(-)	(-)	(-)	(-)
Cerebellar atrophy	(+)	(+)	100%	(-)	(-)	(-)	(-)	35.71%	(-)	(-)	(-)	(-)	(-)
Nerve conduction abnormalities	(+)	(+)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Anticipation phenomenon	(+)	(+)	100%	(-)	(-)	(-)	(-)	35.71%	(-)	(-)	(-)	(-)	(-)
Reduced Penetrance	(+)	(-)	NP	(-)	(-)	(-)	(-)	NP	(-)	(-)	(-)	(-)	(-)
Peripheral neurophaty	NA	(-)	NP	66%	(-)	(-)	(-)	NP	66.6%	(-)	(-)	(-)	(-)
High transaminases	NA	NP	NP	66%	9%	NP	NP	NP	NP	NP	NP	NP	N

Note. NA= No applicable, NV=Not valuable, NP=Not proven. (+)=Found feature. (-)=Feature not foun

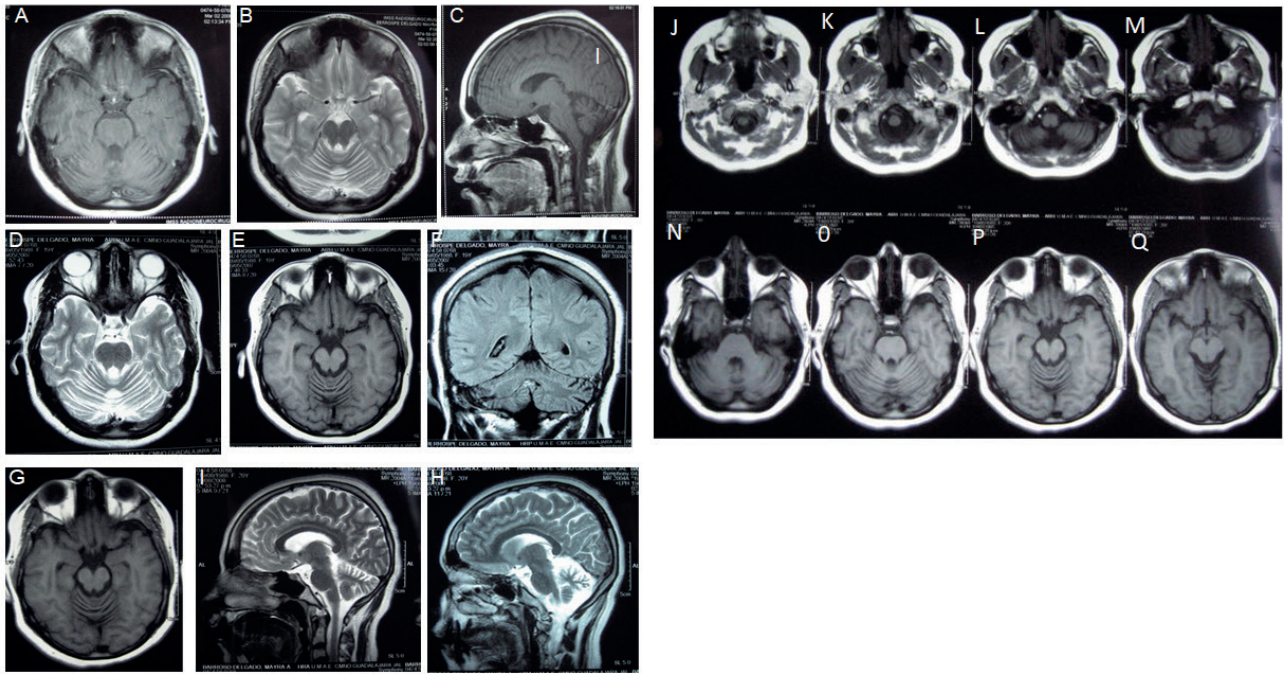

Figure 1 MRI findings in the patient with SCA10. The brain scan T1 shows atrophy of the cerebellum, brain stem and vermix, with ventriculomegaly. A-C Proposita initial study. D-E. One year evolution. G-H. Two years evolution. J-Q panoramic view of the spinocerebellar damage, two years later of evolution

mother using a GeneCatcher (Invitrogen) kit, which was used for conventional PCR amplification with the primers, flanking the pentanucleoitde ATTCT in intron 9 of the gene ATXN102. The PCR product was analyzed by poliacrilamide electrophoresis at 12%, which revealed that the proposita showed a band of 202 bp which corresponded to an allele with 19 normal repeats, and an allelic variant with a higher undetermined number of repeats. The mother presented an homozygote genotype 19/19 indicating that she did not carried an abnormal expansion of the pentanucleotide (figure 2A). To calculate the size of the expanded allele, the proposita's sample was analyzed by single chain conformational polymorphism (SCCP) and isoelectro-focus through the Phastsystem equipment, which revealed that de PCR denatured sample presented a band or approximately 5 Kb, so the proposita genotype was 19/Exp (figure 2B). This indicated that she is carrier of a massive expansion of 5000 repeats, and corroborates de diagnosis of SCA10 by the gold standard RED2. This technique discarded abnormal CAG repeats for SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17 and DRLPA. As a control, 304 healthy non-related individuals were analyzed, between 20 and 55 years, in whom no abnormal expansions ATTCT were detected. The allelic and genotype frequencies within a normal range are presented on table 2.

DISCUSSION

This study corresponds to the first case of SCA10 which presents convulsive crisis, suicide behavior, akinetic parkinsonism, hypothyroidism, galactorrhea associated with an allele of high penetrance expansion, approximately 5000 repeats, from paternal transmission apparently. Previously in SCA10 has been reported convulsive crisis in carriers with massive expansions with interruptions of the pentanucleotide repeats[4-11], similar to the present caser, which presented a higher number of repeats.

Behavioral disturbances in the patient with SCA10 can be related with cortical, raphe nucleus and midbrain atrophy, features that were found at the brain scan MRI, since serotonergic and dopaminergic pathways are affected 12. These pathways are affected in patients with suicide behavior, as in the present case. Deregulation of E46L with GNB2 plays a crucial role in dopaminergic neuritogenesis, as well as in oncogenesis, which can be explained also the prolactinomas and the galactorrhea. Therefore, when the patient was treated with risperidone and bromocriptine, she improves her psychiatric troubles and regularized her menstrual disturbances and the galactorrhea, since the risperidone is a selective antagonist that has high affini-

Table 2 Distribution of genotypes and alleles of the *ATXN10* pentanucleotide in healthy population of northwestern México

Genotype	n	%	Alleles	n	%
9/19	1	0.33	9	1	0.16
11/13	4	1.31	11	16	2.63
11/11	4	1.31	12	4	0.66
11/12	4	1.31	13	16	2.63
13/14	8	2.63	14	73	12.00
13/16	4	1.31	15	96	15.79
14/14	20	6.58	16	54	8.88
14/15	20	6.58	17	36	5.92
14/16	4	1.31	18	50	8.22
14/24	1	0.33	19	107	17.59
15/15	24	7.89	20	80	13.15
15/16	20	6.57	21	32	5.26
15/17	8	2.63	22	20	3.28
16/16	2	0.68	23	4	0.65
16/17	16	5.26	24	19	3.12
16/18	6	1.97	Total Chromosomes	608	
17/18	12	3.95			
18/19	32	10.52			
19/19	15	4.93			
19/20	32	10.52			
19/21	12	3.95			
20/20	24	7.89			
21/22	16	5.26			
21/23	4	1.31			
22/24	4	1.31			
24/24	7	2.30			
Total subjects	304				

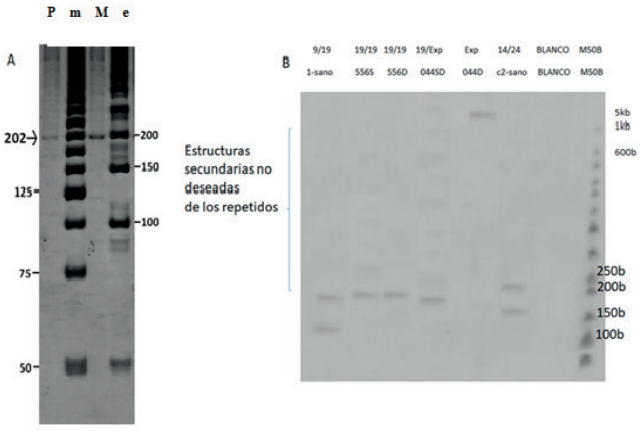

Figure 2

Figure 2A The PCR product was submitted to PAGE electrophoresis in 12% polyacrylamide gel amplifying products of the *ATXN10* gene.. In lane 2 from left to right corresponds to the *proposita* **(P)**. In lane 2 **(m)** to a molecular weight marker 25 b ladder. Lane 3 **(M)**, the *proposita's* mother; and lane 4 **(e)** to a 50b ladder. The arrow points to a 202 bp band corresponding to 19 pentanucleotide repeats. Figure 2B. PAGE electrophoresis on 12% homogeneous gel, using SCCP and electrofocusing. In lane 1 from left to right corresponds to the sample with normal genotype 9/19. The lane 2 corresponds to the sample 556S from the proposita's mother (secondary structures are observed) undenatured and with normal genotype 19/19. The lane three corresponds to the previous sample but denatured (without secondary structures), 556D with 19/19 genotype. Undenatured 044 SCA10 genotype 19/5000Exp. c2-healthy 14/24. M50B= Marker of 50bp. Note: The pentanucleotide expansion done by conventional PCR with the primers ATX10-F5´–AGAAAA-CAGATGGCAGAATGA–3´yATX10R5´GCCTGGGC AACATA GAGA-GA–3´2. Amplification conditions; initial temperature of 94°C, 5 min that denatures template DNA, 30 cycles (94°C per 40s, 60°C per 40s, 72°C 1 min), and additional extension of 72°C, 10 min, 4°C indefinitely2. For isoelectrofocusing the application of the sample was in phase 1.2. Phases; Phase 1. 1-10Vh, 10mA, 2.5W, 5oC, 60Vh. Phase 1.2 100V 1mA, 2.5W, 5oC, 10Vh. Phase 1.3 300V, 10mA, 2.5W5oC, 250Vh. Phase 1.4 300V 10mA, 2.5W, 5oC. All the electrophoresis gels were stained with silver nitrate.

ty for 5-HT2 receptors and the bromocriptine an agonist of the dopamine through the D2 receptors that regulate prolactin secretion[12].

Hypothyroidism in cases with SCA10 may be related to dysregulation of ataxin-10 due to a dominant negative effect of ataxin-10 associated to abnormal expansions during the morphogenesis, inducing dyshormonogenesis[10], which is evident in the laboratory exams of the proposita as a cause of hypothyroidism.

The field of ataxin-10 in psychiatric and endocrine disorders is a frontier study. More clinical studies must be done in patients with SCA10 in order to expand the phsychiatric and endocrinological phenotype, and analyze the expression of ataxin-10 in animal models and in pituitary and hypothalamic cell cultures to corroborate the endocrine pathophysiology.

Furthermore, an alternative method for rapid diagnosis for SCA10 is presented, SCCP by isoelectric focusing, since

the electrophoresis by this method allows to diagnose cases of exponential expansions up to 5kb, validated by the PCR-RED. On the basis that long expansions have a different structure than abnormal expansions, so at the electrophoresis presents a different migration, as we found, however we detected alleles longer than those reported in Mexico and in other populations[2,15], which may be due to the heterogeneity of the locus.

CONCLUSION

A new case of SCA10 is presented with early onset suicide crisis, and severe neurologic damage, akinetic parkinsonism and endocrinopathies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Ashizawa T, Matsuura T. Spinocerebellar ataxia type 10 (SCA10): a disease caused by a novel pentanucleotide repeat expansion. Rinsho Shinkeigaku. 2001;41(12):1120-2.

2. Matsuura T, Yamagata T, Burgess L, Rasmussen A, Grewal P, Watase K, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet. 2000;26(2):191-4.

3. Almeida T, Alonso I, Martins S, Ramos E, Azevedo L, Ohno K, et al. Ancestral origin of the ATTCT repeat expansion in spinocerebellar ataxia type 10 (SCA10). PLoS One. 2009;4(2):e4553.

4. Teive H, Muñoz R, Raskin S, Arruda W, de Paola L, Werneck L, et al. Spinocerebellar ataxia type 10: Frequency of epilepsy in a large sample of Brazilian patients. Mov Disord. 2010;25(16):2875-8.

5. Matsuura T, Ranum L, Volpini V, Pandolfo M, Sasaki H, Tashiro K, et al. Spinocerebellar ataxia type 10 is rare in populations other than Mexicans. Neurology. 2002;58(6):983-4.

6. Moro A, Puppi R, Camargo C, Moscovich M, Farah M, Teive A. Is fatigue an important finding in patients with spinocerebellar ataxia type 10 (SCA10)? Clin Neurosci 2020;71:150-152.

7. Moro A, Muñoz R, Moscovich M, Arruda W, Raskin S, Silveira L, et al. Nonmotor Symptoms in Patients with Spinocerebellar Ataxia Type 10. Cerebellum. 2017;16(5-6):938-944.

8. Grewal R, Achari M, Matsuura T, Durazo A, Tayag E, Zu L, et al. Clinical features and ATTCT repeat expansion in spinocerebellar ataxia type 10. Arch Neurol. 2002;59(8):1285-90.

9. McFarland K, Liu J, Landrian I, Zeng D, Raskin S, Moscovich M, et al. Repeat interruptions in spinocerebellar ataxia type 10 expansions are strongly associated with epileptic seizures. Neurogenetics. 2014;15(1):59-64.

10. Ramirez S, Cruz D, Flores L, Baltzar L, Sánchez M, Elzaurdin R. Genetic Perspective of the Congenital Hypothyroidism, ATXN10 a Candidate Gene. Annals Thyroid Res. 2018; 4(2):155-155.

11. McFarland K, Liu J, Landrian I, Gao R, Sarkar P, Raskin S, et al. Paradoxical effects of repeat interruptions on spinocerebellar ataxia type 10 expansions and repeat instability. Eur J Hum Genet. 2013;21(11):1272-6.

12. Muñoz IA. Neurobiología del suicidio. CT10 2018: 17-47

13. Nascimento F, Rodriguesa V, Pellosoa F, Ferreira C, Camarg H, Morod A, et al. Spinocerebellar ataxias in Southern Brazil: Genotypic and phenotypic evaluation of 213 families. Clinical Neurology and Neurosurgery. 2019; 184: 105427.

14. Teive H, Roa B, Raskin S, Fang P, Arruda W, Correa N, et al. Clinical phenotype of Brazilian families with spinocerebellar ataxia 10 Neurology. 2004;63(8):1509-12.

15. Goel D, Suroliya V, Shamim U, Mathur A, Faruq M. Spinocerebellar ataxia type 10 (SCA10): Mutation analysis and common haplotype based inference suggest its rarity in Indian population. eNeurological Sci. 2019; 17(1): 100211.

16. Rasmussen A, Matsuura T, Ruano L, Yescas P, Ochoa A, Ashizawa T, et al. Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. Ann Neurol. 2001; 50(4): 234-239.