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Short communication

The unique co-occurrence of spinocerebellar ataxia type 10 (SCA10) and Huntington disease

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ABSTRACT

We present a unique thirty-nine year old woman with both Huntington's disease (HD) and spinocerebellar ataxia type 10 (SCA10). She has 48 CAG repeats in the HD gene and 2511 ATTCT repeats in the ATX10 gene. Although both conditions are repeat expansion diseases they are thought to have quite different pathogenic mechanisms. The symptomatic age of onset in this patient (mid30s) is within the expected range for her repeat expansion sizes for each condition, but we discuss the evidence that the two conditions may interact to produce a more severe cognitive phenotype than would be expected for either of the conditions independently. The subject has Amerindian background on the maternal side from Colombia, South America, thus adding a 5th country expressing SCA10, all with Amerindian ancestry.

1. Introduction

Very occasionally a single individual will have a pathogenic mutation in more than one gene associated with a neurodegenerative disease. Such rare cases provide a unique opportunity to determine the consequences of experiencing the simultaneous affect of two different pathogenic mechanisms occurring in the same brain. We report here the co-occurrence of both Huntington disease (HD) and spinocerebellar ataxia type 10 (SCA10) in a 39 year old woman. The onset of symptoms, clinical manifestations and especially the neuropsychological features are described. The molecular mechanisms underlying each disease are thought to be distinct. Although the age of onset of her symptoms fell within the expected range, her marked cognitive decline may represent an additive effect of the two disease processes.

2. Methods

The subjects was interviewed and examined and medical records reviewed in the University of Washington Neurogenetics Clinic under a protocol approved by the Human Subjects Review Committee.

3. Case report

The patient is a 39 year old woman born in Colombia South America of a Native American/Amerindian mother and a white European Australian father. She was homeless as a young child, suffered from malnutrition and lived in an orphanage until age 8. At that age she was adopted by a couple from the United States and moved to live with them in the state of Washington. At the time of her adoption she had been assessed and been found to be of normal intelligence. She graduated from public high school taking both regular and special education classes. She was physically small, hyperactive, and said to have attention deficit disorder. She was athletic and played successfully on a softball team. Following school she was employed in several retail stores and used a cash register. In her mid-thirties she began to have difficulties with both cognition and coordination resulting in loss of employment. Her cognitive decline became very noticeable to her family and friends. She was once thought to be intoxicated because of slurred speech. She also began to experience frequent blinking episodes associated with decreased alertness and responsiveness. An EEG was normal but she was placed on levetiracetam resulting in a decreased frequency of the episodes. She was also noted to have chorea, dystonia and gait ataxia. A brain MRI showed mild midline cerebellar atrophy and a battery of genetic tests was obtained. The Huntington disease test was positive with 48 CAG repeats in the HD gene and surprisingly the SCA10 test was also positive with 2511 ATTCT repeats in the ATX10 gene (abnormal > 800).

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At age 38 she had formal neuropsychological testing (Table 1). Verbal IQ was 67, performance IQ 72, and full scale IQ 66. Her performance was impaired in numerous subcategories of the testing including vocabulary, information, comprehension, arithmetic, digital span, letter number sequencing, picture completion, block design, coding, symbol search and trail making. Her few strengths were limited to visual attention. During the testing she demonstrated mild depression and a high level of anxiety.

Examination at age 39 showed that she was 4′9″ (144.78 cm) tall weighing 104 lbs (47.2 kg). She was able to carry on a reasonable conversation, provide an accurate history and follow all instructions. She had diminished facial expression. She had dysarthria but could be understood when speaking slowly. She had continuous but small amplitude chorea of her trunk and all four limbs. There was dystonic posturing of upper limbs, left more than right. Gait was mildly wide based, stiff and unsteady with a negative Romberg test. She could not tandem walk. Range of eye movements was full but smooth pursuit was broken and saccades had mildly increased latency and slow velocity. She could not suppress head movements during eye movement examination. There was no evidence of vestibular failure on head impulse test or on visual acuity with and without head shake. There was no motor impersistence on tongue protrusion. Rapid alternating movements of fingers and hands were mildly impaired and she could initiate but not complete the Luria test. Strength was retained and deep tendon were hyperactive in all four limbs including bilateral Hoffman's and bilateral unsustained ankle clonus. Plantar reflexes were withdrawl with a possible left extensor response. Sensation was intact to pinprick and vibration.

4. Discussion

SCA-10 is a late onset spinocerebellar ataxia described in South American native Indian populations initially in Mexico [1,2] and later in Brazil [3], Argentina [4] and Venezuela [5]. The disease presents at an average age of 35 with gait ataxia with subsequent development of dysarthria, dysphagia and upper limb ataxia [6]. In families from Mexico, Argentina and Venezuela but not Brazil seizures develop shortly after the onset of disease [3]. It is inherited in an autosomal dominant fashion by an ATTCT pentanucleotide intronic repeat expansion in the ATXN10 gene on chromosome 22 [7]. Huntington's disease is also autosomal dominant and associated with a CAG trinucleotide exonic repeat in the huntingtin gene. The mechanisms by which DNA repeat expansions cause pathology in each condition remain only partially understood. In SCA10 the intronic AUUCU repeat is transcribed and spliced, binds to hnRNPK and may cause neuronal apoptosis by massive translocation of PKCδ to mitochondria and caspase 3 activation [8]. HD is thought to result from toxic gain of function of the mutant HTT protein producing nuclear protein aggregates and mitochondrial dysfunction focused especially on vulnerable medium spiny neurons in the striatum [9]. No neuropathology has been reported in SCA10 but the disease process clearly affects both the cerebellar and cortical neuronal systems. If the two diseases share pathogenic mechanisms it might be postulated that disease severity would be more aggressive over and above the contribution of each single disease in a dually affected person. We therefore compared our patient's clinical picture with what might be expected from each disease independently.

Normal repeats sizes for SCA-10 are usually between 10 and 29 repeats [7]. Intermediate alleles have been described between 280 and ~800 repeats and fully penetrant alleles from 800 to 4500. Haplotype studies have confirmed that there is an ancestral founder effect in the Amerindian population [10]. Our patient's expansion of 2200 is in the middle of the range of those affected and her presentation is also in the midrange for this disease (Fig. 1) so presentation with symptoms of ataxia and epilepsy from the mid 30s is entirely consistent with the description of the progression of this disease in the literature. It is interesting to note that the presence of epilepsy in this patient groups her with the Mexican/Venezuelan/Argentinian phenotype rather than the Brazilian phenotype. These symptoms would be unlikely to occur in adult HD patients, although seizures are relatively common in juvenile HD presenting before the age of 10 [11]. Similarly the presentation in the mid 30s with chorea, difficulty suppressing head movements during saccades and breakdown of alternating eye movements would be entirely consistent with the expected course of disease for 48 CAG repeat huntingtin [12]. Therefore the age at onset and constellation of physical symptoms and signs are expected for each individual disease.

However, the cognitive decline and broad range of intellectual disability in the present individual are more severe than would be expected in the early stages of either disease. Table 1 shows that she was severely

Table 1
Neuropsychological testing (age 38).

Full Scale IQ (WAIS III)	66
Verbal IQ	67
Performance IQ	72
Wide Range Achievement Test (WRAT-4)	Percentile
Word reading	18
Sentence comprehension	3
Spelling	9
Math	1
Reading	6
Wechsler Memory Scale — III	
Family pictures I (focused visual attention)	63
Family pictures II (sustained visual attention)	50
Faces I (focused visual attention)	16
Face II (sustained visual attention)	63
Logical Memory I (immediate recall)	2
Logical Memory II (delayed recall)	16
VPA I (immediate auditory recall)	5
VPA II (delayed auditory recall)	1
Letter–number sequencing	2
Spatial span	1
Trail Making A (88s)	Impaired
Trail Making B (162s)	Impaired
Controlled Oral Word Assoc. (COWAT)	<1
Wisconsin Card Sort (WCST)	<1
Sentence Repetition Test (7/14)	7
Boston Naming (29/60)	<1
Hooper Visual Organization (VOT 18.5/30)	Impaired
Stroop color test	<1
Manual finger tapping	
Left	Impaired
Right	Impaired
Beck Depression Inventory (14/63)	Mild
Beck Anxiety Inventory (27/63)	Severe

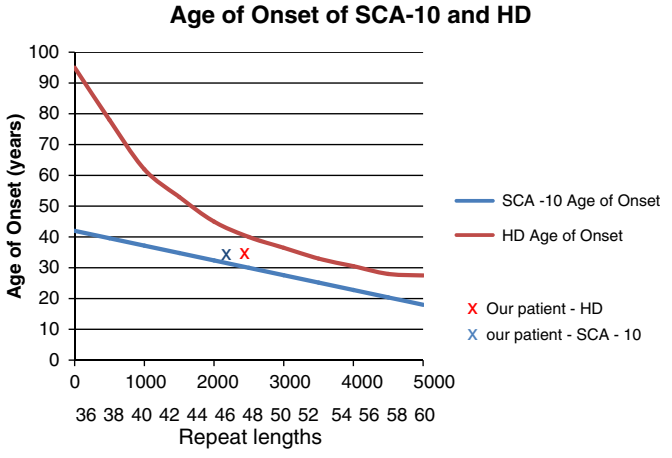

Fig. 1. Age of symptom onset in patient with both SCA-10 (blue X) and Huntington's disease (red X) compared with curves showing age of onset as a function of ATTCT repeat size (SCA-10, blue line) [8] and CAG repeat size (HD, red line) [12].

Table 2
Additive severity in co-occurrence of neurogenetic diseases.

Neurogenetic disease co-occurrences	Additive severity?
Trisomy21/myotonic dystrophy (DM1) [17]	No
Friedreich's Ataxia/NF1 [18]	No
CMT1A/CMTX1 [19]	Yes
CMT1A/myotonic dystrophy (DM1) [19]	Yes
HNPP/adrenomyeloneuropathy [19]	Yes
SCA6/EA2*	Yes
PSEN1 (FAD)/PRNP [20]	Yes
HD/SCA10 (This report)	Yes

Key: NF1 = neurofibormatosis 1; CMT = Charcot–Marie–Tooth; HNPP = hereditary neuropathy with pressure palsies; EA2 = episodic ataxia 2; PSEN 1 = presenilin 1; FAD = familial Alzheimer disease; PRNP = prion protein.
* Personal patient of co-author TDB.

impaired (frequently below the 5th percentile) across a wide spectrum of cognitive abilities including comprehension, vocabulary, mathematics, immediate and delayed recall and executive functions. She only functioned in the normal range on tests of visual attention. This is more severe than expected for early stage HD as well as SCA10. Cognitive disability has been described in some cases of SCA10, more commonly in the Mexican families than the Brazilian families. It is reported in about 10–20% of the Mexican cases (some with personality changes) and 7% of the Brazilian cases [13,14]. However these cases have not been associated with such a rapid decline near the age of symptom onset. Thus we conclude that at the cognitive level of expression the two disease processes is likely to be having an amplifying effect on each other in our present case. The results in Table 1 represent one of the most detailed descriptions of cognitive disability in a subject with SCA10.

In addition, it should be noted that two copies of the CAG expansion causing HD (homozygosity for HD) do not generally produce a more severe clinical phenotype than heterozygosity for the disease mutation [15,16]. Thus, in the present case the apparent additive effect of the SCA10 ATTCT expansion is different from having an additional HD CAG expansion.

Table 2 reviews our experience (and one additional example) of individuals who have inherited two separate neurogenetic diseases. For those in which underlying disease mechanisms are probably very different (trisomy 21/DM1 and Friedreich ataxia/NF1) there seems to have been no extra effects over and above the features that each disease independently would be expected to cause. However in those in which disease mechanisms affect the same or similar aspects of the nervous system (peripheral neuropathies, cerebellar ataxia, and cortical dementias) the severity of the combined diseases is usually more than would be expected in one disease alone. The present report adds SCA10 and HD to the latter category.

Finally the finding of SCA-10 in a patient from Colombia confirms that this disease is likely to be present throughout South and Central America originating in the Amerindian community.

Following submission of this paper a report has appeared of a 54 year old man of Mexican and Native American ancestry with repeat expansions in both SCA2 and SCA10 who had onset of ataxia in his early 40s and has mild cognitive deficits [21].

Conflict of interest

TDB receives licensing fees from Athena Diagnostics, Inc.

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