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Case Series

Clinical phenotyping aids genotype prediction in hereditary ataxia: a case series

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ABSTRACT

Hereditary cerebellar ataxias comprise a heterogeneous group of neurodegenerative disorders with overlapping clinical manifestations, often making accurate bedside diagnosis challenging. Careful clinical phenotyping remains essential to guide targeted genetic testing, particularly in resource limited settings. We retrospectively reviewed five patients with progressive hereditary ataxia at a tertiary care neurology centre. Detailed clinical evaluation, pedigree analysis, and comprehensive neurological examination were performed, followed by molecular genetic confirmation. The cohort included two patients with Spinocerebellar Ataxia Type 2 (SCA2), one with Spinocerebellar Ataxia Type 3 (SCA3/Machado–Joseph disease), and two with Friedreich's ataxia (FRDA). Distinctive clinical features were highly suggestive of the underlying genotype prior to molecular confirmation. Markedly slowed saccades and hyporeflexia characterized SCA2, whereas SCA3 demonstrated external ophthalmoparesis, pyramidal signs, and lower motor neuron involvement with preserved saccadic velocity. Both FRDA patients exhibited posterior column sensory loss with generalized areflexia and extensor plantar responses, consistent with corticospinal tract involvement. Pedigree analysis differentiated autosomal dominant from autosomal recessive inheritance, and repeat expansion size correlated with earlier disease onset and greater clinical severity. A systematic bedside assessment incorporating oculomotor findings, reflex pattern, sensory examination, pyramidal and lower motor neuron signs, and pedigree analysis enables reliable phenotypic differentiation among hereditary ataxias before genetic confirmation. Such an approach facilitates targeted molecular testing and optimizes diagnostic evaluation, particularly in resource-constrained settings.

Keywords: Hereditary ataxia, Spinocerebellar ataxia, SCA2, SCA3, Machado–Joseph disease, Friedreich's ataxia, ATXN2, ATXN3, FXN, Repeat expansion, Genotype-phenotype correlation

INTRODUCTION

Hereditary ataxias comprise a diverse group of progressive neurodegenerative disorders characterized by cerebellar dysfunction, resulting in gait instability, limb incoordination, dysarthria, and oculomotor abnormalities.[1] They are genetically heterogeneous and may be inherited in autosomal dominant, autosomal recessive, X-linked, or mitochondrial patterns.

Advances in molecular genetics have identified more than 50 subtypes of spinocerebellar ataxia (SCA), while Friedreich's ataxia (FRDA) remains the most common inherited autosomal recessive ataxia worldwide.[2] Among the autosomal dominant ataxias, SCA2 and SCA3 are caused by pathogenic CAG trinucleotide repeat expansions in the ATXN2 and ATXN3 genes, respectively, leading to toxic polyglutamine protein accumulation and neuronal degeneration. Both disorders exhibit genetic anticipation, with larger repeat expansions

generally associated with earlier disease onset and greater clinical severity. In contrast, FRDA results from biallelic GAA repeat expansions within intron 1 of the FXN gene, causing frataxin deficiency, mitochondrial dysfunction, and multisystem involvement affecting the cerebellum, dorsal root ganglia, posterior columns, corticospinal tracts, peripheral nerves, myocardium, and skeletal system.[3] Despite distinct genetic mechanisms, these disorders share several overlapping clinical manifestations, making early clinical differentiation challenging. Nevertheless, careful bedside assessment of inheritance pattern, ocular motor abnormalities, deep tendon reflexes, pyramidal signs, sensory involvement, lower motor neuron features, and associated skeletal abnormalities often provides valuable diagnostic clues that guide targeted genetic testing. This approach is particularly important in resource-limited settings, where indiscriminate multigene testing may not be feasible. In this case series, we describe five genetically confirmed patients with hereditary ataxia, including two cases of SCA2, one case of SCA3, and two cases of FRDA. By correlating detailed clinical findings with molecular genetic results, we highlight the distinctive phenotypic features of these disorders and emphasize the value of systematic bedside examination in narrowing the differential diagnosis before genetic confirmation.

CASE SERIES

Case 1: SCA 2 with markedly slow saccades

A 32-year-old man presented with a 2-year history of progressive gait and limb ataxia,intention tremor and dysarthria.family history showed autosomal dominant inheritance with genetic anticipation.examination revealed pancerebellar signs,markedly slow hypometric saccades,ankle hyporeflexia and mild distal large fibre sensory loss.genetic testing demonstrated a pathogenic ATXN2 CAG expansion (22/41 repeats), confirming SCA2.

Case 2: Friedrich's ataxia with prominent sensory ataxia and skeletal abnormalities

Case 2 represents a genetically confirmed case of Friedreich's ataxia (FRDA) featuring a classic sensorimotor phenotype. Symptom onset at age 18 with prominent sensory ataxia manifesting as worsening balance in darkness, positive Romberg physiology, and unnoticed footwear slippage highlights early sign dorsal column and peripheral nerve dysfunction. Key diagnostic features on examination included skeletal deformities (bilateral pes cavus and hammer toes), lateral gaze-evoked nystagmus with broken pursuits (notably without saccadic slowing), intact motor power with bilateral ankle dorsiflexion/inversion weakness, and profound posterior column sensory loss.

Deep tendon reflexes were absent at the knees and ankles, whereas upper limb reflexes were preserved. Bilateral extensor plantar responses indicated corticospinal tract involvement. Sensory examination revealed impaired vibration sense and fine touch in lower limbs, consistent with posterior column dysfunction. Molecular genetic testing provided definitive verification by identifying a homozygous GAA repeat expansion (>65 repeats) in intron 1 of the FXN gene.

Case 3: Advanced Friedreich's ataxia with severe disability

Case 3 illustrates the natural progression and long-term burden of Friedreich's ataxia. Presenting at 40 years of age with a 25-year disease duration, this patient exhibited severe multisystem impairment. Symptoms began at age 15 with progressive gait instability, advancing over a decade to complete loss of independent ambulation. Examination demonstrated advanced skeletal and neuromuscular involvement, including right mid-thoracic scoliosis, distal lower-limb muscle wasting, and loss of vibration and proprioception ascending to the mid-calf. A defining feature distinguishing this recessive phenotype from dominant SCAs was global areflexia. Oculomotor examination revealed horizontal gaze-evoked nystagmus, delayed saccade initiation, and square-wave jerks. This case highlights the relentless progression of FRDA toward severe mobility restriction and prominent skeletal deformities.

Case 4: SCA2 with marked genetic anticipation

a 27-year-old man presented with a 6-year history of progressive gait and limb ataxia, falls, dysarthria and distal paraesthesia. A three-generation pedigree showed autosomal dominant inheritance with progressively earlier onset across generations. examination revealed pancerebellar signs, markedly slow hypometric saccades, ankle hyporeflexia, and mild large fibre sensory loss. Genetic testing demonstrated pathogenic ATXN2 CAG expansion confirming SCA2.

This stepwise drop in onset age across successive generations is a hallmark of CAG repeat expansions. On clinical examination, the patient demonstrated a pure cerebellar syndrome accompanied by early dorsal column sensory neuropathy (impaired lower-limb vibration and proprioception). Notably, pyramidal signs were absent, and deep tendon reflexes and plantar responses remained entirely normal, distinguishing this presentation from SCA-3 or FRDA.

Case 5: SCA 3 with pyramidal and lower motor neuron features

Case 5 highlights an atypical, complex neurodegenerative phenotype characterized by overlapping cerebellar, pyramidal, and lower motor neuron (LMN) dysfunction. The patient presented with progressive gait ataxia, strained/spastic dysarthria, marked weight loss 15-20 kg, and prominent muscle wasting.

Table 1: Clinical characteristics and phenotypic distribution of patients with hereditary ataxia.

Parameter / clinical feature	N	%
Demographics and patient profile		
Male sex	4	80
Female sex	1	20
Consanguinity	0	0
Right-handedness	4	80
Left-handedness	1	20
Inheritance pattern		
Autosomal dominant (AD)	3	60
Autosomal recessive (AR)	2	40
Core cerebellar signs		
Progressive gait imbalance / ataxia	5	100
Cerebellar dysarthria	5	100
Dysmetria / dyssynergia	5	100
Intention tremor	3	60
Dysdiadochokinesia	5	100
Truncal ataxia	1	20
Pyramidal & motor signs		
Hyperreflexia (DTR ≥ +3)	1	20
Extensor plantar responses	3	60
Areflexia / Absent dtrs	4	80
Flexor plantar responses	2	40
Muscle wasting / atrophy	2	40
Lower motor neuron features (fasciculations/myokymia)	1	20
Sensory and peripheral involvement		
Sensory neuropathy (tingling / numbness)	4	80
Proprioceptive / posterior column deficit	2	80
Footwear slippage / sensory ataxia	4	80
Oculomotor abnormalities		
Gaze-evoked Nystagmus	2	40
Broken pursuit / saccadic dysfunction	2	40
Ophthalmoparesis / upgaze restriction	1	20
Skeletal deformities		
Pes cavus / hammer toes	1	20
Scoliosis	1	20
Provisional / final diagnosis		
SCA-2	2	40
Friedreich's Ataxia (FRDA)	2	40
SCA-3	1	20

*Values are presented as count (N) and percentage (%) unless otherwise specified (n=5). N= number of patients

Neurological examination confirmed prominent LMN involvement—including facial myokymia, eyebrow and lower lip fasciculations, tongue fasciculations, and intrinsic hand muscle atrophy alongside brisk reflexes (+3 to +4), patellar/ankle clonus, and extensor plantar responses. Oculomotor testing showed upgaze restriction and gaze-evoked nystagmus.

DISCUSSION

A total of five patients with genetically confirmed hereditary ataxia managed at tertiary care hospital were evaluated. The cohort comprised four males and one female, with a mean age of onset of 21.6 years (range: 15-21 years for early-onset cases, and 23.2 years for the advanced SCA3 presentation). The cases were classified into three distinct genetic etiologies: Spinocerebellar Ataxia Type 2 (SCA2; n=2), Friedreich's Ataxia (FRDA; n=2), and Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (SCA3/MJD; n=1).

Genotype-phenotype correlation

Distinct neuro-ophthalmologic and systemic markers differentiated the cohorts: Oculomotor Signatures: Marked slowing of horizontal and vertical saccades was uniquely observed in both SCA2 cases (Cases 1 and 4). In contrast, the SCA3 patient (Case 5) demonstrated a limitation of upward gaze and external ophthalmoparesis but with preserved saccadic velocity.

Neuromuscular and pyramidal involvement

The SCA3 patient demonstrated a classical multisystem phenotype, displaying distinct lower motor neuron (LMN) features such as tongue and facial fasciculations and generalized amyotrophy-concurrently with upper motor neuron signs (spasticity, hyperreflexia, and clonus). FRDA patients strictly presented with loss of deep tendon reflexes, extensor plantar responses, and prominent skeletal deformities (pes cavus, scoliosis).

This retrospective observational study highlights the diverse phenotypic landscape and strong genotype-phenotype correlations among patients presenting with hereditary ataxias in a tertiary care center in Western India. Autosomal dominant spinocerebellar ataxias (SCA2 and SCA3) and autosomal recessive Friedreich's ataxia (FRDA) present overlapping cerebellar syndromes but can be reliably differentiated using targeted clinical clues.[4]

Oculomotor control as a diagnostic discriminator

The evaluation of saccadic eye movements emerged as a critical clinical differentiator within our dominant ataxia cohort. Both SCA2 cases demonstrated markedly slowed saccades, which served as the primary clinical indicator prompting ATXN2 testing. Pathologically, this corresponds to early neurodegeneration within the paramedian pontine reticular formation (PPRF) and burst neurons. Conversely, our SCA3 patient exhibited external ophthalmoparesis but with completely preserved saccadic velocity, highlighting that oculomotor pathway involvement differs fundamentally between these two expansions.[5]

Genetic anticipation in trinucleotide repeat disorders

Our study clearly illustrates the phenomenon of genetic anticipation in autosomal dominant repeat expansions. In the SCA2 cohorts, consecutive generations demonstrated a clear trend toward earlier disease onset and increased clinical severity.

This was further substantiated by comparing the molecular metrics of Case 1 and Case 4. The patient with the longer pathogenic CAG repeat expansion (23/45 repeats vs. 22/41 repeats) experienced a more rapid progression of upper limb incoordination and early-onset disability, directly aligning with established global datasets indicating that larger expanded alleles compromise protein stability more aggressively.[6]

Systemic and multisystem manifestations

The presentation of FRDA in our series (Cases 2 and 3) underscores its classification as a systemic, multisystem disease rather than a pure cerebellar disorder. The combination of early-onset ataxia with posterior column dysfunction (loss of vibration and position sense), areflexia, and skeletal pathologies (pes cavus and progressive thoracic scoliosis) forms a recognizable clinical constellation. Mechanistically, the biallelic GAA expansion in the FXN gene leads to a severe deficiency of frataxin, a mitochondrial protein, causing iron overload and mitochondrial dysfunction that targets the dorsal root ganglia, posterior columns, and skeletal development.[7]

Meanwhile, our advanced SCA3 case showcased a prominent "type 2" Machado-Joseph phenotype, where cerebellar signs are heavily accompanied by extrapyramidal, pyramidal, and explicit LMN signs (such as facial and tongue fasciculations).[8]

The primary limitations of this study include its retrospective design and the small sample size, which restricts generalizability across wider demographics.

CONCLUSION

In conclusion, while molecular confirmation via repeat-expansion analysis remains the gold standard for diagnosing hereditary ataxias, careful clinical documentation of oculomotor metrics, reflex profiles, and systemic skeletal anomalies allows for highly accurate diagnostic stratification and targeted genetic testing.

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