



Spinocerebellar Ataxia 8: Variable Phenotype And Unique Pathogenesis

Amitabh Gupta M.D. Ph.D.¹ and Joseph Jankovic M.D.²

¹Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21205

²Department of Neurology, Baylor College of Medicine, Houston, TX 77030



BACKGROUND

SCA8 is an autosomal dominant triplet repeat expansion disorder, affecting a gene on chromosome 13q21, that is regarded as distinct from most other inherited ataxias.

Life span is not affected by the disease and there does not appear to be a direct relationship between the triplet repeat length and disease severity or progression. Further, there is contraction of the triplet repeat length with paternal transmission and the gene product consists of a non-coding RNA. Most notably, the phenotype of SCA8 is unusually variable and symptoms often occur episodically. As a result, diagnosis of SCA8 not infrequently evades detection, which necessitates a better clinical definition of this disease.

Here, we (1) assess 3 new cases of genetically verified spinocerebellar ataxia (SCA8) for the presence of unusual or novel symptoms and (2) systematically analyze our cases and those reported in the literature for a symptom constellation that may provide a better framework for diagnosing SCA8 clinically.

Basic demographic data and clinical features in previously reported and current SCA8 cases

Cases	Age of onset	Age of evaluation	Gender (female)	Repeat length	Cerebellar signs				Pyramidal signs			
					Nystagmus	Dysarthria	Limb ataxia	Gait ataxia	Hyperreflexia	Extensor plantar	Sensory signs	Cognitive impairment
Day	13-65 (35;16)	34-68	–	107-127 (116;6.3)	8/11	11/11	11/11	10/11	8/11	2/11	5/11	0/11
Ikeda	20-73 (54;20)	–	4/6	89-155 (106;24.4)	4/6	6/6	6/6	6/6	1/6	0/6	2/6	0/6
Silveira	0-31 (21;10)	12-46	3/7	100-152 (119;19.9)	–	7/7	–	6/7	–	–	–	3/7
Juvonen	–	15-51	9/15	85-345 (159;65)	5/15	14/15	12/15	13/15	9/15	5/15	4/15	6/15
Jardim	31	41	1/1	104	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1
Sempere	–	59	1/1	112	0/1	1/1	1/1	1/1	1/1	0/1	0/1	–
Brusco	15-35 (34;22)	–	3/4	89-97 (94;3.1)	2/4	3/4	3/4	4/4	2/4	2/4	1/4	0/4
Topisirovic	38	43	0/1	100	–	1/1	1/1	1/1	1/1	–	–	0/1
Tazon	12-50 (27;20)	25-76	1/3	111-124 (119;6.8)	2/3	3/3	3/3	3/3	–	0/2	0/2	0/1
Izumi	10-63 (34;19)	–	9/15	86-221 (141;41.6)	–	–	–	15/15	9/15	1/15	–	4/15
Schoels	2-59 (30;17)	4-73	–	111-212 (158; 39.3)	4/11	10/11	9/11	10/11	2/11	–	–	3/11
Felling	2	3	0/1	238	0/1	0/1	1/1	0/1	0/1	0/1	0/1	–
Torrens	13-70 (42;14)	21-76	7/13	92-200+	4/13	10/13	10/13	13/13	5/13	1/13	5/13	9/13
Gupta	26-38 (32;6)	31-40	3/3	79-593	0/3	1/3	1/3	2/3	1/3	1/3	1/3	1/3
Total	0-73 (34;17)	12-76	32/54	79-593 (140;65)	30/68	68/76	58/69	85/91	39/81	12/71	19/56	26/88
Total (%)	–	–	–	–	44	89	84	93	48	17	34	30

This table depicts reported symptomatic SCA8 cases in chronological order. Clinical features were determined by either symptom or clinical finding.

Number pairs not in parentheses = the first number indicates the number of affected individuals, the second number represents the number of total SCA8 patients in that study
Number pairs in parentheses = the first number indicates mean, the second number indicates standard deviation

METHODS

Three cases of diagnosed SCA8, with triplet repeat lengths of 79, 126 and 593, respectively, were assessed by chart review and video tape analysis. Their phenotypic spectrum, disease course, family history, and co-morbidities were compared with reported cases (see video demonstrations and figure).

RESULTS

- In addition to ataxia, the following clinical features were present in our cases to a variable degree: fatigue, migraines, myoclonous, dystonia, dysarthria, behavioral and cognitive problems, a variety of sensory symptoms, seizure-like episodes without EEG correlates, hyperreflexia, and urinary symptoms.
- Compared to cases from the literature (figure), many symptoms overlapped, but analysis of our and previously reported cases did not reveal a common symptom constellation that is confined and consistent enough to point to the diagnosis of SCA8.
- Interestingly, a triad of myoclonus, migraine, and ataxia was prominent in all 3 of our cases. Myoclonus occurred early in the disease course, consistent with the MRI not showing cerebellar atrophy.
- Two of the three cases had a distinctly episodic disease course.
- Fatigue and dystonia were present in each case, with fatigue posing a challenging management problem and dystonia, albeit of variable clinical significance, clearly recognizable in the neurological exam.

CONCLUSIONS

SCA8 is a disease with marked clinical variability. We propose to consider the ataxia-myoclonus-migraine triad as a presentation form of SCA8, with myoclonus indicating early disease. Validation of this notion awaits data on the symptoms triad in additional cases, as reported cases failed to address those symptoms rigorously.

Given that the non-coding RNA may affect calcium channel function (non-coding RNA -> antisense RNA-> inhibition of KLHL1 -> abnormal P/Q calcium channel function), the presence of migraines, ataxia and episodic symptomatology in SCA8 could point to a clinical and perhaps pathogenic overlap with the channelopathies (i.e.EAT2). Further studies will provide improved insight into pathogenesis and clinical definition of this neurological disorder.

REFERENCES

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