Abstract

Spinocerebellar ataxias (SCAs) comprise a group of complex and heterogeneous hereditary neurodegenerative disorders characterized by cerebellar ataxia, with ophthalmoplegia, pyramidal and extrapyramidal features, peripheral neuropathy, motor neuron disease, pigmentary retinopathy, epilepsy, and dementia in varying proportions. Cognitive impairment is not frequent in SCAs but is rarely noticed since it gets camouflaged behind the exorbitant ataxic manifestations of the disease. The exact incidence and extent of cognitive impairment in these rare disorders are not known due to the heterogeneity between different SCA types and different modalities of testing employed in different studies. Through our review, we have summarized the cognitive aspects of SCA and can safely conclude that cognitive dysfunction is common in some SCA types when compared to others. Not only is it important to appreciate its presence as a symptom complex in SCA but also is the need to actively search and treat it to improve the patients’ quality of life.

Keywords: Ataxia, cognition, SCA

Introduction

Spinocerebellar ataxias (SCAs) comprise a group of complex and heterogeneous hereditary neurodegenerative disorders characterized by cerebellar ataxia with ophthalmoplegia, pyramidal and extrapyramidal features, peripheral neuropathy, motor neuron disease, pigmentary retinopathy, epilepsy, and dementia in varying proportions. These are rare (incidence between 1 and 5 per 100,000) disorders having the onset between 30 and 50 years of age. Although ataxia is a criterion standard, different SCA types have variations in their pathological topography leading to differences in their clinical, radiological, and cognitive profile at a subtype level. The exact incidence and extent of cognitive impairment in these rare disorders are not known due to the heterogeneity between different SCA types and different modalities of testing employed in different studies.

Cognitive Impairment in Spinocerebellar Ataxia

SCAs are characterized by the involvement of prominent cerebellar but extra-cerebellar structures as well. As a result, various plausible theories have been postulated regarding cognitive dysfunction in the same.

Cerebellar cognitive affective syndrome

The use of anatomical investigations and trans-synaptic tracing techniques in primates provided the first evidence of the presence of cortico-ponto-cerebello-thalamo-cortical loops, which form the basis for the proposition that the cerebellum plays a role in cognition. These loops connect the prefrontal cortex (executive function) with the cerebellar dentate nuclei and associated posterolateral cerebellar cortex. The same loops have since been demonstrated in human beings through diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) studies.

Schmahmann and Sherman in their landmark article provided the framework for the constellation of non-motor symptoms associated with localized cerebellar insult and termed it as “cerebellar cognitive affective syndrome (CCAS).” These include impairments in executive functions, language, visuospatial functions, and personality. These were associated with posterior cerebellar lesions and the manifestations were ascribed to disruption of circuitry linking the same to cerebral cortical association areas and paralimbic regions.

Prefrontal Cortico-Striato-Thalamo-Cortical loops

Since many SCAs like SCAs 2, 3, and 17 have concomitant parkinsonism, an analogous involvement of these loops was
suggested. The orbitofrontal and dorsolateral prefrontal cortex relay in the striatum and the involvement of this circuitry may be the cause of cognitive dysfunction in these SCA types. This usually presents with a typical “frontal-subcortical” profile of cognitive deficits.

**Basal forebrain nuclei cholinergic projections**

The major cholinergic input to the hippocampus, amygdala, and neocortex is provided by the projections from the basal forebrain nuclei. Their involvement was hypothesized when the evidence of dysfunction in verbal and visual memory was documented in the SCA patients, which remains unexplained by (a) and (b). It was thought to be contributory in a way similar to that seen in Alzheimer’s disease. Cortical cholinergic denervation has since been demonstrated predominantly in SCAs1 and 2.

**Direct cortical involvement**

Radiological and post-mortem assessments from a few studies have revealed that certain SCA types (like SCA12) directly affect the neurons of the association cortex leading to neuronal loss and cortical atrophy.

**Crossed cerebellar diaschisis**

Crossed cerebellar diaschisis (CCD) cannot be ruled out as a definite contributor for cognitive impairment in the SCA patients in the absence of functional imaging as unilateral cerebellar damage has been shown to have accompanied decreased blood flow in the contralateral basal ganglia and frontoparietal cortex.

**Testing Cognitive Impairment in SCA**

A few studies have looked at cognitive dysfunction in SCA but have suffered from many confounding factors.

First is the inconsistency of test selection from the battery of standard neuropsychological tests available. Not only does this result in difficulty in comparing study results and conducting a meta-analysis but also sometimes the choice of the test is not sensitive enough to identify the cognitive deficit in cerebellar dysfunction alone.[8]

Sometimes, the tests chosen might depend on the rapid motor or verbal response, which may be hampered in ataxic patients leading to them being wrongly classified in the impaired cognition group.[9] Examples of such tests include the Tower of London and Tower of Hanoi tests, which are timed and require a substantial degree of motor accuracy.

The Mini-Mental State Examination (MMSE) is one of the most commonly used screening tools for cognitive impairment in research and clinical practice, but it is insensitive to executive dysfunction, and therefore, is likely to underestimate the cognitive dysfunction of the SCA patients, if used alone.[10]

The cognitive tests that are not dependent on the performance speed pressure and do not place undue importance on accuracy and motor/visual speed can be used to study cognition in ataxic subjects including those with SCA. Examples of such tests include the Wisconsin Card Sorting Test and Raven’s Progressive Matrices. Even Trail making or Stroop tests may be used (although they are timed tests per se) because their timed internal component can be used to account for the articulatory and upper limb motor deficiencies along with visual scanning.

**Individual SCAs** Cognitive domains found affected in various studies in different SCA types have been mentioned in Table 1.

**SCA1**

It is caused by CAG repeat expansion on the ataxin-1 gene resulting in an expanded polyglutamine tract of 39–91 residues, and histopathologically, it is associated with marked atrophy of the brainstem, cerebellar cortex, and deep nuclei, red nuclei, VPL Ventroposterolateral nucleus of the thalamus, and Betz cells of the motor cortex. Of particular relevance to our review is the fact that there is also a loss of cholinergic forebrain nuclei and volume loss of the frontal and prefrontal cortex.[9] However, radiologically, brainstem atrophy is present but cortical atrophy is absent.

Cognitive changes have been described in 5–25% of the patients of SCA1, and are usually seen in the advanced stages of the disease.[11] Overall, they were found to have mild cognitive impairment with executive dysfunction being the most common. This dysfunction rarely progressed to dementia. Social cognition was not affected.[9]

**SCA2**

It is caused by CAG repeat expansion on the ataxin-2 gene resulting in an expanded polyglutamine tract of 33–200 residues and its histopathological involvement resembles SCA1.[32-34] However, the radiological brainstem atrophy is more severe than SCA1 and a “hot cross bun” sign can be seen in 25% of the patients.[35] It is the commonest SCA in India and the frequency of cognitive impairment is estimated to be between 5 and 19% among different studies.[13,31] The cognitive dysfunction profile is “frontal-subcortical” and supportive of the hypothesis of neuronal involvement extending beyond the cerebellum, involving the pallidolysian system and the substantia nigra.[13]

**SCA3 ( Machado-Joseph disease)**

It is caused by CAG repeat expansion on ataxin-3 gene resulting in an expanded polyglutamine tract of 51–89 residues,[36] and histopathologically, it prominently affects the deep cerebellar nuclei and the red nucleus, while the remaining structures are less severely involved and the basal forebrain cholinergic circuit being spared.[29] Like SCA1, radiologically, the cerebral cortex does not show atrophy despite severe neuronal loss, and the “hot cross bun” pattern may be seen in 1% of the cases.[35] Cognitive impairment has traditionally been considered to be uncommon in this type and individual studies have also not reported a significant occurrence of dementia. Some studies have found the presence of impairments in executive function, visual attention, verbal, and visuospatial memory.[14,15,37] Functional MRI studies revealed hand-movement-related cerebellar activation impairment but the absence of significant reduction of signal in the cerebellar cortex or cerebellar nuclei.[38]
Table 1: SCA studies on cognition with the domains affected and their correlations

| Publication               | SCA type          | Number of patients | Cognitive domains studied                                      | Affected                                                                                                                               | Correlation                                                                 |
|---------------------------|-------------------|--------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Kish et al., 1988[8]      | SCA1              | 14                 | IQ, attention, verbal and non-verbal intellectual ability, memory, and executive function | Mildly reduced verbal memory and executive dysfunction - 11/14 cases                                                                               |
| Bürk K, et al., 2001[11]  | SCA1              | 14                 | Verbal memory and executive dysfunction                           | None                                                                                                                                   |
| Storey et al., 1999[10]   | SCA2              | 8                  | Frontal lobe function- verbal fluency, Stroop and WCST          | None                                                                                                                                   |
| Gambardella et al., 1999[23] | SCA2          | 17                 | Conceptual reasoning, memory, language, depression               | Conceptual reasoning- WCST Decrease in the saccadic velocity | Disease duration for both                                                    |
| Bürk K, et al., 1999[13]  | SCA2              | 17                 | IQ, attention, verbal, visuospatial memory, and executive functions | Verbal memory and executive dysfunction                                                                                                |
| Maruff P, et al., 1996[26] | SCA3              | 6                  | Visual attention, learning and visual memory                     | None                                                                                                                                   |
| Zawacki TM, et al., 2002[14] | SCA3          | 6                  | MMSE and other neuropsychological batteries                     | Relative impairments on timed verbal attention tasks and verbal fluency, executive impairments, depression | Verbal fluency correlated with ataxia severity                                |
| Kawai Y, et al., 2004[19] | SCA3              | 16                 | Executive functions, visuospatial perception, and verbal memory, attention, immediate and delayed recall, logical thinking function, and orientation function | None                                                                                                                                   |
| Braga-Neto P, et al., 2012[16] | SCA3          | 38                 | MMSE, all cognitive domains                                     | None                                                                                                                                   |
| Roeseke S, et al., 2013[17] | SCA3              | 11                 | All cognitive domains                                           | None                                                                                                                                   |
| Bürk K, et al., 2003[19]  | SCA1-2, 3        | 14                 | IQ, attention, executive function, verbal and visuospatial memory | None                                                                                                                                   |
| Mar J, et al., 2014[19]   | SCA1-2           | 11                 | All cognitive domains                                           | None                                                                                                                                   |
| Ma J, et al., 2014[19]    | SCA1-2, 3        | 14                 | IQ, attention, executive function, verbal and visuospatial memory | None                                                                                                                                   |
| Ma J, et al., 2014[19]    | SCA1-2           | 11                 | All cognitive domains                                           | None                                                                                                                                   |
| Globas C, et al., 2003[29] | SCA6              | 12                 | IQ, attention, verbal and visuospatial memory as well as executive function | Mild impairment in most categories but none reached a statistical significance | None                                                                       |
| Suenaga M, et al., 2007[31] | SCA6          | 18                 | Attention, verbal memory, visuospatial memory, and executive function | Verbal fluency and immediate visual memory | None                                                                       |
| Cooper FE, et al., 2010[22] | SCA6            | 27                 | Verbal working and immediate visuospatial memory correlated with disease duration for SCA6 | None                                                                                                                                   |
| van Gaalen J, et al., 2014[32] | SCA6          | 29                 | Language functions                                              | Mild-to-moderate linguistic impairment, most distinct on the writing and comprehension sub-tests | Severity of ataxia                                                          |
| Rentiya ZS, et al., 2017[24] | SCA6          | 21                 | General intelligence (MMSE), executive function, visuospatial perception, and verbal memory, attention, immediate and delayed recall | Verbal working and immediate visuospatial memory correlated with disease duration for SCA6 | None                                                                       |
| Klinke I, et al., 2010[23] | SCA1, 2, 3, 6    | 32                 | All cognitive domains                                           | SCA1s 2 and 3: Poor frontal attention and executive deficits SCA6: Mild impairment | Age of onset; disease duration                                               |
| Agrawal A, et al., 2021[30] | SCA12            | 30                 | All cognitive domains                                           | None                                                                                                                                   |
| Bruni AC, et al., 2004[27] | SCA17            | 16                 | All cognitive domains                                           | None                                                                                                                                   |
SCA6
It is an uncommon type of SCA and occurs due to a short (20–33) CAG repeat expansion on the CACNA1A subunit of the PQ-type calcium channel. It usually has a later age of onset as compared to the other SCAs. Histopathologically, there is a Purkinje cell loss in the cerebellar cortex and Betz cells in the motor cortex with mild variable neuronal loss in the other regions. However, there is no macroscopic cerebral atrophy and radiology typically reveals pure cerebellar atrophy. A detailed neuropsychological assessment revealed marked impairment of the visuospatial memory, semantic and phonemic fluency tasks with some impairment on the response inhibition test and executive function. The intellectual functioning was not impaired. The functional MRI studies revealed hand-movement-related cerebellar activation impairment and significant reduction of signal in the cerebellar cortex or cerebellar nuclei.

SCA12
It is caused by CAG repeat expansion in the promoter region of the PPP2R2B gene on chromosome 5q32, presenting characteristically with action and head tremors with dysarthria. Neuropathologically, marked atrophy of the cerebral cortex and Purkinje cells with less prominent pontine and cerebellar atrophy, and radiologically, varying degrees of mild-to-moderate cerebral and cerebellar atrophy (cerebral > cerebellar) are found. Cognitive impairment was found to be a part of the disease spectrum and characterized by executive dysfunction and disability in new learning ability even early in the disease course. This did not correlate with the patient’s age, age at onset, disease duration, or CAG repeat length. DTI in SCA12 pedigree patients revealed microstructural changes in the white matter of the brain even in presymptomatic patients. This was found to first occur in the cerebral cortex and cerebellar vermis.

SCA17
It is caused by CAG repeat expansion on the gene encoding TATA Box-Binding Protein (TBP) resulting in an expanded polyglutamine tract of 41–63 residues, and histopathologically, prominently involves the cerebellar and cerebral cortex, basal ganglia, and medial thalamus. Radiologically, it displays both marked cerebral and cerebellar with mild brainstem atrophy. Psychiatric features like hallucinations and personality changes along with early and severe dementia are common. It usually starts with behavioral complaints and decreased verbal fluency, finally culminating in a frontotemporal dementia pattern of cognitive impairment.

Conclusion
Cognitive impairment is not infrequent in SCAs but is rarely noticed since it gets camouflaged behind the exorbitant ataxic manifestations of the disease. This subsequent paucity of testing leads to a false sense of cognitive well-being when there is none present. This problem is further compounded by the absence of consistent neuropsychological assessment tools and studies with an adequate number of patients who have been longitudinally studied over long periods to understand the pattern of cognitive disease progressions. Also, cognitive assessment of SCAs has predominantly been done in relatively commoner types. However, we can safely conclude that cognitive dysfunction is commoner in some SCA types when compared to others and it is important to appreciate its presence as a symptom complex in SCA patients with the need to actively search and treat it to improve the patients’ quality of life.

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Conflicts of interest
There are no conflicts of interest.

References
1. Van de Warrenburg BPC, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER, Ippel PF, et al. Spinocerebellar ataxias in the Netherlands: Prevalence and age at onset variance analysis. Neurology 2002;58:702-8.
2. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: A systematic review of prevalence studies. Neuroepidemiology 2014;42:174-183.
3. Grafman J, Litvan I, Massaquoi S, Stewart M, Sirigu A, Hallett M, et al. Cognitive planning deficit in patients with cerebellar atrophy. Neurology 1992;42:1493-6.
4. Akshoomoff NA, Courchesne E. A new role for the cerebellum in cognitive operations. Behav Neurosci 1992;106:731-8.
5. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain J Neurol 1998;121:561-579.
6. Maruff P, Tyler P, Burt T, Currie B, Burns C, Currie J. Cognitive deficits in Machado-Joseph disease. Ann Neurol 1996;40:421-7.
7. Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, et al. Cognitive deficits in progressive supranuclear palsy, Parkinson’s disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. J Neurol Neurosurg Psychiatry 1994;57:79-88.
8. Kish SJ, Schut L, Simmons J, Gilbert J, Chang LJ, Rebbetoy M. Brain acetylcholinesterase activity is markedly reduced in dominantly-inherited olivopontocerebellar atrophy. J Neurol Neurosurg Psychiatry 1988;51:544-8.
9. Lindsay E, Storey E. Cognitive changes in the spinocerebellar ataxias due to expanded polyglutamine tracts: A survey of the literature. Brain Sci 2017;7:83.
10. Storey E, Forrest SM, Shaw JH, Mitchell P, Gardner RJM. Spinocerebellar ataxia type 2: Clinical features of a pedigree displaying prominent fronto-executive dysfunction. Arch Neurol 1999;56:43-50.
11. Bürk K, Böscher S, Globas C. Cognitive deficits in Spinocerebellar Ataxia 1 (SCA1). Eur Neurol 2001;46:43-8.
12. Gambardella A, Annesi G, Bonomo F, Spadafora P, Valentino P, Pasqua AA, et al. CAG repeat length and clinical features in three Italian families with spinocerebellar ataxia type 2 (SCA2): Early impairment of Wisconsin card sorting test and saccade velocity. J Neurol 1998;245:647-52.
13. Bürk K, Globas C, Bosch S, Graber S, Abele M, Brice A, et al. Cognitive deficits in spinocerebellar ataxia 2. Brain 1999;122:769-77.
14. Zawacki TM, Grace J, Friedman JH, Sudarsky L. Executive and emotional dysfunction in Machado-Joseph disease. Mov Disord 2002;17:1004-10.
15. Kawai Y, Takeda A, Abe Y, Washimi Y, Tanaka F, Sobue, G. Cognitive impairments in Machado-Joseph disease. Arch Neurol 2004;61:1757-60.
16. Braga-Neto P, Felicio AC, Pedrosa JL, Dutra LA, Bertolucci PHF, Gabbai AA, et al. Clinical correlates of olfactory dysfunction in spinocerebellar ataxia type 3. Parkinsonism Relat Disord 2011;17:353-6.
17. Roeseke S, Filla I, Heim S, Amunts K, Helmstaedter C, Willner U, et al. Progressive cognitive dysfunction in spinocerebellar ataxia type 3. Mov Disord 2012;27:4303-10.
Cognition in trinucleotide repeat SCAs

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Clinical features, neurogenetics and neuropathology of the
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Moderate expansion of a normally biallelic
Morphological basis for the spectrum of clinical deficits in

32. Imbert G, Saudou F, Yvert G, Devys D, Trottier Y, Garnier JM, Bürk K. Cognition in hereditary ataxia. Cerebellum 2007;6:280‑6.
31. Bürk K. Cognition in trinucleotide repeat SCAs
18. Bürk K, Globas C, Bösch S, Klockgether T, Zühlke C, Daum I, et al. Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. J Neurol 2003;250:207-11.
19. Ma J, Wu C, Lei J, Zhang X. Cognitive impairments in patients with spinocerebellar ataxia types 1, 2 and 3 are positively correlated to the clinical severity of ataxia symptoms. Int J Clin Exp Med 2014;7:5765-71.
20. Globas C, Bösch S, Zühlke C, Daum I, Dieghans J, Bürk K. The cerebellum and cognition. Intellectual function in spinocerebellar ataxia type 6 (SCA6). J Neurol 2003;250:1482-7.
21. van Gaalen J, de Swart BMJ, Oostvseen J, Knuijt S, van de Warrenburg BPC, Kremer BPH. Language impairment in cerebellar ataxia. Mov Disord 2014;29:1307-12.
22. Rentiya ZS, Jung BC, Bae J, Liszewski CM, Fishman A, Du AX, et al. Selective patterns of cognitive impairment in spinocerebellar ataxia type 6 and idiopathic late-onset cerebellar ataxia. Arch Clin Neuropsychol 2018;33:427-36.
23. Klinke I, Minnerop M, Schmitz‑Hübsch T, Hendriks M, Klockgether T, Wüllner U, Kremer B. Cognitive deficit in spinocerebellar ataxia type 6. Behav Neurol 2010;23:3-15.
24. Rentiya ZS, Jung BC, Bae J, Liszewski CM, Fishman A, Du AX, et al. Cognitive impairment in spinocerebellar ataxia type 1. Nat Genet 1993;4:221‑6.
25. Klinke I, Minnerop M, Schmitz‑Hübsch T, Hendriks M, Klockgether T, Wüllner U, et al. Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3 and 6. Cerebellum 2010;9:433‑42.
26. Agrawal A, Kaur H, Agarwal A, Nehra A, Pandey S, Garg A, et al. Cognitive impairment in spinocerebellar ataxia type 12. Parkinsonism Relat Disord 2021;85:52-6.
27. Bruni AC, Takahashi‑Fujigasaki J, Maltecca F, Foncin JF, Servadio A, Casari G, et al. Behavioral disorder, dementia, ataxia, and rigidity in a large family with TATA box‑binding protein mutation. Arch Neurol 2004;61:1314-20.
28. Orr HT, Chung MY, Banfi S, Kwiatkowski TJ Jr, Servadio A, Beaudet AL, et al. Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat Genet 1993;4:221-6.
29. Seidel K, Siswanto S, Brunner HP, den Dunnen W, Korf HW, Rub U. Brain pathology of spinocerebellar ataxias. Acta Neuropathol 2012;124:1-21.
30. Rub U, Schols L, Paulson H, Auberger G, Kermer P, Jen JC, et al. Clinical features, neurogenetics and neuropathology of the polyglutamine spinocerebellar ataxias type 1, 2, 3, 6 and 7. Prog Neurobiol 2013;104:38-66.
31. Bürk K. Cognition in hereditary ataxia. Cerebellum 2007;6:280‑6.
32. Imbert G, Saudou F, Yvert G, Devys D, Trottier Y, Garnier JM, et al. Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. Nat Genet 1996;14:285‑91.
33. Sanpei K, Takano H, Igarashi S, Sato T, Oyake M, Sasaki H, et al. Identification of the spinocerebellar ataxia type 3 gene using a direct identification of repeat expansion and cloning technique, DIRECT. Nat Genet 1996;14:277-84.
34. Pulst SM, Nechiporuk A, Nechiporuk T, Gispert S, Chen XN, Lopes‑Cendes I, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet 1996;14:269‑76.
35. Lee YC, Liu CS, Wu HM, Wang PS, Chang MH, Soong BW. The ‘hot cross bun’ sign in the patients with spinocerebellar ataxia. Eur J Neurol 2009;16:513‑6.
36. Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, et al. CAG expansions in a novel gene for Machado‑Joseph disease at chromosome 14q32.1. Nat Genet 1994;8:221-8.
37. Rossi M, Perez‑Lloret S, Doldan L, Cerrutti D, Balej J, Millar VP, et al. Autosomal dominant cerebellar ataxias: A systematic review of clinical features. Eur J Neurol 2014;21:607‑15.
38. Stefanescu MR, Dohu M, Maderwald S, Thüring M, Minnerop M, Beck A, et al. Structural and functional MRI abnormalities of cerebellar cortex and nuclei in SCA3, SCA6 and Friedreich’s ataxia. Brain 2015;138:1182‑97.
39. Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, et al. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A‑voltage‑dependent calcium channel. Nat Genet 1997;15:62‑9.
40. Currie S, Hadjivassiliou M, Craven IJ, Wilkinson ID, Griffiths PD, Hoggard N. Magnetic resonance imaging biomarkers in patients with progressive ataxia: Current status and future direction. Cerebellum 2013;12:245‑66.
41. Geschwind DH, Perlman S, Figueroa KP, Karrim J, Baloh RW, Pulst SM. Spinocerebellar ataxia type 6. Frequency of the mutation and genotype‑phenotype correlations. Neurology 1997;49:1247‑51.
42. Holmes SE, O’Hearn E. Expansion of a novel CAG repeat in the 5’ region of protein phosphatase 2A PR55B is associated with spinocerebellar ataxia type 12. Nat Genet 1999;23:391‑92.
43. Srivastava AK, Choudhry S, Gopinath MS, Roy S, Tripathi M, Brahmachari SK, et al. Molecular and clinical correlation in five Indian families with spinocerebellar ataxia 12. Ann Neurol 2001;50:796‑800.
44. Srivastava AK, Takkar A, Garg A, Faruq M. Clinical behaviour of spinocerebellar ataxia type 12 and intermediate length abnormal CAG repeats in PPP2R2B. Brain 2017;140:27‑36.
45. Li H, Ma J, Zhang X. Diffusion tensor imaging of spinocerebellar ataxia type 12. Med Sci Monit 2014;20:1783‑91.
46. Koide R, Kobayashi S, Shimohata T, Ikeuchi T, Maruyama M, Saito M, et al. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA‑binding protein gene: A new polyglutamine disease? Hum Mol Genet 1999;8:2047‑53.
47. Lasek K, Lencer R, Gaser C, Hagenah J, Walter U, Wolters L, et al. Morphological basis for the spectrum of clinical deficits in spinocerebellar ataxia 17 (SCA17). Brain 2006;129:2341‑52.