

MAGNETIC RESONANCE IN THE DIAGNOSIS OF THE MOST
COMMON FORMS OF SPINOCEREBELLAR ATAXIAPRIMENA MAGNETNE REZONANCIJE U DIJAGNOSTICI
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Abstract

Spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominant ataxias characterized by a dominantly progressive evolution of the cerebellar syndrome and other extra-cerebellar symptoms and signs. Today there are approximately 40 genetic SCAs and this review aims to describe the clinical picture and magnetic resonance imaging (MRI) findings of the most common SCA subtypes in Europe and Serbia. This is a group of polyglutamine diseases caused by mutations resulting from the expansion of the CAG repeats and accompanied by the loss of neural volume mainly of the cerebellum and the spinal cord. Magnetic resonance has a vital role in the diagnosis since it excludes structural damage as one of the potential causes of ataxia. In addition to this, the loss of volume, as demonstrated by MRI, serves as a biomarker that helps to monitor the natural progression of different subtypes of the disease. Typical findings in these MRI scans include cortico-cerebellar atrophy, spinal cord atrophy, olivopontocerebellar atrophy, and different combinations of the said atrophies. Unfortunately, there are no distinct pathognomonic MRI signs or combinations of signs to facilitate diagnosis. There are, however, similarities in the MRI findings of some of the SCA subtypes, especially at disease onset. The ability to differentiate one pattern of atrophy from another and observe other clinical characteristics can have an important role and can be of significant help in the diagnostic process.

Keywords:

spinocerebellar
ataxia,
magnetic resonance
imaging,
diagnosis

Sažetak

Spinocerebelarne ataksije (SCA) predstavljaju heterogenu grupu autozomno dominantnih ataksija koje se manifestuju dominantno progresivnim razvojem cerebelarnog sindroma, ali i različitim stepenom prisustva ekstracerebelarnih simptoma i znakova. Danas postoji preko 40 genetski determinisanih SCA, a u ovom radu su opisane klinička slika i nalazi magnetne rezonancije (MR) najčešćih SCA u Evropi i Srbiji. To su bolesti koje su prouzrokovane mutacijama u vidu ekspanzija CAG ponovaka, pripadaju poliglutaminskim bolestima, a karakteriše ih gubitak neuralnog volumena pre svega cerebeluma i kičmene moždine. Magnetna rezonancija u dijagnostičkom postupku ima suštinski važnu ulogu kako bi se isključila strukturna oštećenja, koja mogu biti uzrok ataksije. Pored toga gubitak volumena verifikovan primenom MR predstavlja na neki način biomarker, kojim se može pratiti prirodna progresija različitih podtipova ove bolesti. Nalazi MR u grupi ovih oboljenja se karakterišu kortiko-cerebelarnom atrofijom, atrofijom kičmene moždine, olivoponto-cerebelarnom atrofijom ili različitim kombinacijama istih. Nažalost, ne postoji patognomoničan MR znak ili kombinacija znakova, pored toga postoje i značajna preklapanja MR nalaza u pojedinim podgrupama SCA, pogotovu u početku bolesti. Ipak poznavanje određenih razlika u obrascu atrofije moždanih struktura, uz prisustvo drugih kliničkih karakteristika značajno nam može pomoći u dijagnostičkom usmeravanju.

Ključne reči:

spinocerebelarna ataksija, magnetna rezonancija, dijagnostika

Introduction

Spinocerebellar ataxias (SCA) are a heterogeneous group of hereditary, autosomal dominant (AD) degenerative diseases that mainly affect the cerebellum, its efferent and afferent pathways as well as other structures in the central and peripheral nervous system. While some forms of SCA have an isolated cerebellar syndrome, the majority SCAs exhibit a combination of cerebellar and extra-cerebellar signs. They are characterized by the loss of neural volume mainly in the cerebellum and the spinal cord. This loss that is demonstrated by magnetic resonance imaging (MRI) serves as a kind of biomarker that helps to monitor the natural progression of the different subtypes of the disease (1). Furthermore, MRI imaging has an essential diagnostic role because it helps exclude structural damage as one of the potential causes of ataxia. This includes damage incurred from strokes, tumors, and metabolic and toxic damage. Parameters such as the volume of the posterior cranial fossa, anteroposterior diameter of the pons, and the height and volume of the cerebellum all significantly differ between SCA patients and healthy populations (2).

Typical MRI findings of this group of diseases include cortico-cerebellar atrophy, spinal cord atrophy, olivopontocerebellar atrophy, and different combinations of the aforementioned atrophies. Different patterns of atrophy can help diagnose certain types of SCAs. Also, correlation has been established between the International Cooperative Ataxia Rating Scale (ICARS) and the MRI-demonstrated cerebellar volume (2). Unfortunately, there are no distinct pathognomonic MRI signs or combinations of signs to guide the way, though together with the patient's motor, nonmotor, systemic and ethnic characteristics, MRI findings can point toward genetic diagnosis. Some MRI algorithms typical of particular SCA subtypes can be used to expedite the diagnosis (**table 1**). This is due to the fact that some atrophy patterns occur more frequently in certain SCA subtypes, though that is mainly

true at disease onset - before the neuropathological process is completed (3). Final diagnosis is established with the help genetic testing. In case of the most frequent SCAs, this includes testing for the trinucleotide repeat expansion (SCA 1, 2, 3, 6, 7, 17). Next-generation sequencing (NGS) such as whole exome sequencing, use of panels, and whole genome sequencing have made it possible to determine causative mutation of many other less common variants of SCA that are the result of point mutations (4).

Table 1. MRI features of specific SCA subtypes.

MRI finding	SCA
Isolated cerebellar atrophy	6
Pontine atrophy	3, 7
Olivopontocerebellar atrophy	1, 2
Spinal cord atrophy	3, 7
Cortical atrophy	2, 3
Pontocerebellar, cortical and subcortical atrophy	17
The hot cross bun sign	1, 2, 3, 6, 7

Today there are more than 40 genetic SCAs and this review aims to present MRI features of the most commonly occurring SCAs in Europe and Serbia. These SCAs are mostly due to the CAG trinucleotide repeat expansion in the coding region of the gene that is in charge of a particular polyglutamine sequence, which triggers the protein's toxic effect on the cell. These SCA subtypes (SCA 1, 2, 3, 6, 7, 17) are characterized by various degrees of anticipation. This means that the number of repeats will increase with each new generation, making the onset occur earlier and the disease more severe.

Additionally, the MRI findings of these SCA subtypes show atrophy of the cerebellum as well as different degrees of atrophy in the extra-cerebellar structures (brain stem, basal ganglia, and the cerebral cortex). This

review aims to briefly describe the clinical picture of the most common SCA subtypes and to present their typical atrophy patterns as shown by MRI.

Clinical and neuroradiological characteristics of the most common types of SCA

Spinocerebellar ataxia type 1 (SCA 1)

Spinocerebellar ataxia type 1 is the most commonly occurring type of SCA in Serbia (5). The disease is caused by the mutation resulting from CAG trinucleotide repeat expansion (altogether 39 expansions) in the ATXN1 gene (6.22.3) responsible for ataxin-1 coding, the protein whose cellular role has not yet been fully explained. The clinical picture of this type of ataxia includes impaired walking and standing ability, limb ataxia with dysarthria and oculomotor disorders, and additional noncerebellar signs such as spasticity, hyperreflexia, hyperkinetic movement disorders, dysphagia, dementia and vocal cord paralysis. The onset of the disease usually occurs in the third decade of life. The typical MRI findings show global cerebellar volume loss (**figure 1**), olivopontocerebellar atrophy and a decrease in the white matter volume (6). These changes in the white matter can result in midline T2W hyperintensity in the basis pontis and the hot cross bun sign that appears in multiple system atrophy (7). The supratentorial segment is usually not affected at the onset of the disease, but the volume of the spinal cord is reduced and correlates with the SARA (Scale for Assessment and Rating of Ataxia) score, number of repeats and disease progression (8).

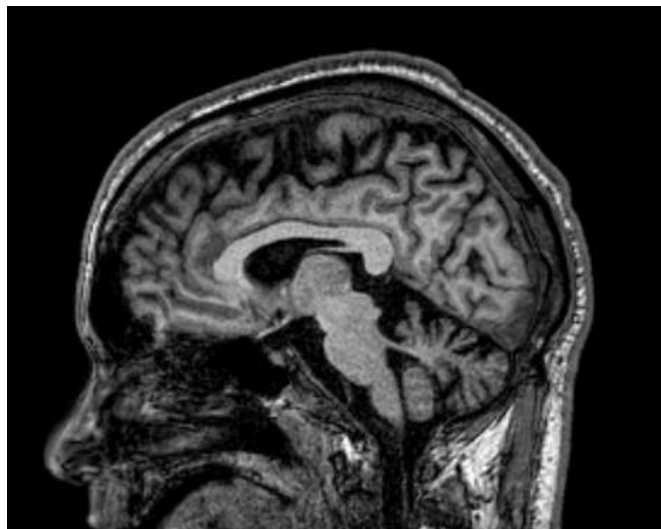


Figure 1. Brain MRI scan of 28-year-old male SCA 1 patient. Disease onset at the age of 27. Sagittal T1-weighted images show a global cerebellar volume loss.

Spinocerebellar ataxia type 2 (SCA 2)

Spinocerebellar ataxia type 2 (SCA 2) is the second most common SCA subtype in Serbia. It is caused by the abnormal expansion of CAG trinucleotide repeats (> 32)

in the coding area of the ATXN2 gene (12q23-q24.1), leading to the abnormal expression of the long polyglutamine sequence in ataxin-2, the protein that becomes toxic and causes neuronal death in the cerebellum, spinal cord and cerebral cortex (9). In addition to the progressive cerebellar syndrome, SCA2 patients also suffer from slower saccadic eye movements, hyporeflexia, tremors, amyotrophy, and parkinsonism. Their MRI points to a typical olivopontocerebellar (**figure 2**) and frontal and temporal lobe white matter and precuneus atrophy, as well as the hot cross bun sign, midline T2W hyperintensity in the basis pontis and of the basal ganglia (7).

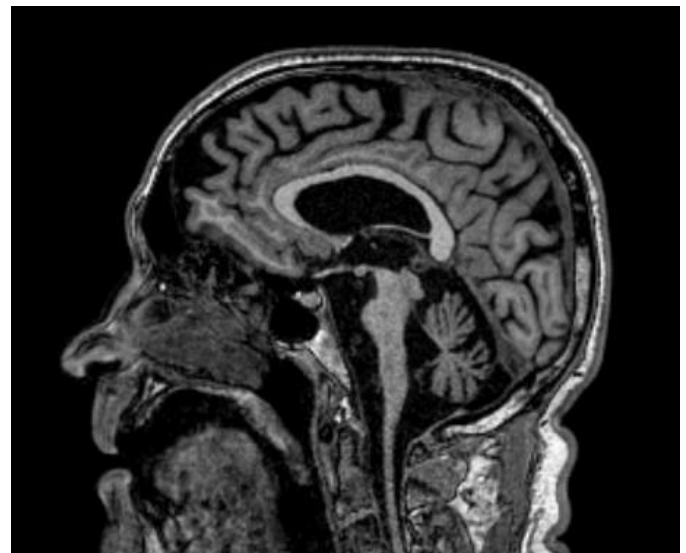


Figure 2. Brain MRI scan of 43-year-old male SCA 2 patient. Disease onset at the age of 30. Sagittal T1-weighted images show a global cerebellar, pontine and spinal cord atrophy.

Spinocerebellar ataxia type 3 (SCA 3) – Machado-Joseph Disease

Though it is rare in Serbia, spinocerebellar ataxia type 3 (SCA 3) is the most commonly occurring type of ataxia in the majority of European countries (5, 10). This subtype also belongs to the group of polyglutamine diseases and is caused by the expansion of CAG repeats (> 50) in the ATXN3 gene (14q21). The symptoms appear between the third and sixth decade of life and include ataxia with dysarthria, eyelid retraction, oculomotor disorders, rigidity and dystonia. The clinical picture depends on the number of repeats, with fewer expansions meaning that ataxia will present itself later in life and be accompanied by peripheral neuropathy. A larger number of repeats will lead to early disease onset and early dystonia and rigidity. A typical MRI finding shows mild vermis and cerebellum atrophy, atrophy of the brain stem with an enlarged IV ventricle, nucleus dentatus volume reduction, atrophy of the middle cerebellar peduncles, and midline T2W hyperintensity in the basis pontis (11).

Spinocerebellar ataxia type 6 (SCA 6)

Spinocerebellar ataxia type 6 (SCA 6) is caused by the expansion of 22 to 30 CAG repeats in the CACNA1A gene. The clinical presentation of this SCA includes ataxia with dysarthria, intention tremor and nystagmus. This is usually a slowly progressing isolated cerebellar syndrome, though pyramidal signs and neuropathy may occasionally appear, with some instances of parkinsonism and dystonia accompanied as well. The disease typically starts in the fifth decade of life and is more frequent in the Japanese population. It accounts for about 10% of idiopathic cerebellar ataxias after the age of 40. MRI shows significant atrophy of the vermis and of the cerebellar hemispheres, but almost no changes in the brain stem (12). This cerebellar atrophy without brain stem atrophy and clear cerebellar signs in the fifth decade of life should raise suspicion of this type of ataxia, which is how MRI can greatly facilitate the diagnostic protocol in case of this SCA.

Spinocerebellar ataxia type 7 (SCA 7)

Spinocerebellar ataxia type 7 is the result of the mutation in the ATXN7 gene caused by the expansion of more than 36 CAG repeats. Due to its distinct anticipation, the onset of the disease can occur at any time between childhood and the sixth decade of life (13). This is a slowly progressing ataxia accompanied by loss of eyesight due to retina pigment degeneration (14). Cognitive impairments and ophthalmoplegia may also appear (15). In this case, the MRI imaging shows prominent atrophy of the pons and the upper part of the vermis (**figure 3**) (16) as well as extra-cerebellar white mass changes, including occipital lobes (17).

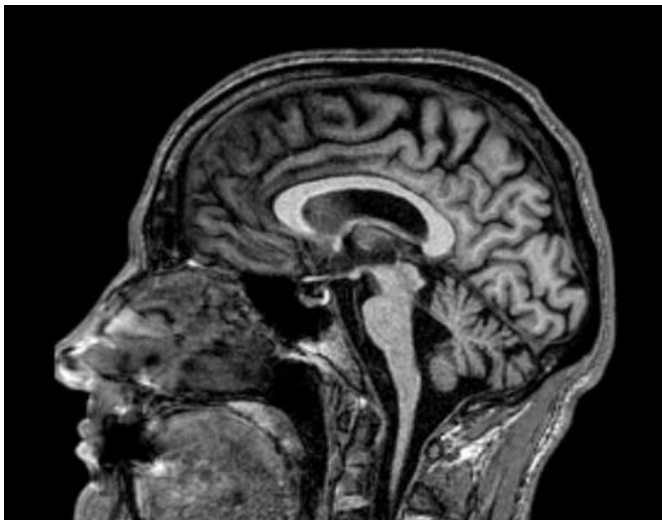


Figure 3. Brain MRI scan of 41-year-old male SCA 7 patient. Disease onset at the age of 30. Sagittal T1-weighted images show a global cerebellar, pontine and spinal cord atrophy.

Spinocerebellar ataxia type 17 (SCA 17)

Spinocerebellar ataxia type 17 (SCA 17) is the result of a mutation caused by the expansion of more than 42 CAG repeats in the TBP (TATA-box-binding protein) transcription factor (18). Affected patients suffer from

dysarthria and chorea (which is why SCA17 can sometimes be confused with Huntington's chorea), which are followed by ataxia, psychiatric disorders, parkinsonism and a cognitive decline. Patients' MRI shows significant cerebellar and global atrophy (19).

There are other advanced neuro visualization methods that can greatly aid in the diagnosis of SCA. These include the following:

- Magnetic spectroscopy, which identifies and analyzes the changing metabolite concentration,
- Functional magnetic resonance, which analyzes changes in the tissue perfusion while conducting a task, and
- Positron emission tomography with 18-fdg, which examines the changes in the tissue glucose metabolism.

However, all the above-mentioned methods have limited use and mainly serve research purposes.

Conclusion

Spinocerebellar ataxias are a heterogeneous group of AD ataxias characterized by dominantly progressive cerebellar syndrome and different extra-cerebellar symptoms and signs. The aim of this review paper was to describe the clinical picture and MRI findings of the most common SCAs, which are polyglutamine diseases caused by mutations resulting from CAG repeat expansion. Although there is certain overlap in the MRI findings of some SCA subtypes (especially at the onset of disease), there are certain differences in the brain structure atrophy pattern that, together with other clinical characteristics, can point the diagnostic process in the right direction.

The clinical research was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (1322/V-11).

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