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# Neuromyelitis optica spectrum standstill in rheumatic systemic autoimmune diseases

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## Abstract

**Background:** Neuromyelitis optica spectrum disorders (NMOSD) are considered as an autoantibody-mediated disorder that targets aquaporin-4 (AQP4); other autoantibodies could be detected in such spectrum of diseases, including anti-nuclear antibody and antibodies to extractable nuclear antigens. Systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and other autoimmune diseases can overlap with NMOSD. We aimed in this review to address the current evidence describing the relation of NMOSD to systemic autoimmunity diseases, its controversy of being co-association or the same etiology, and its practical implications.

**Main body:** The current review was done using a search for related articles or case reports on PubMed until 2019. The keywords included neuromyelitis optica spectrum disorders in combination with autoimmune disease nomenclature. We described the literature background of this controversy, to summarize the evidence of NMOSD relationship to systemic autoimmune diseases.

**Conclusion:** NMOSD associated with systemic autoimmune diseases is more common in SLE and Sjogren's syndrome rather than other autoimmune diseases, frequently affects females more than males; AQP4 antibodies should be tested for all NMOSD like manifestations associated with an autoimmune disorder; however, the clinical diagnosis of NMOSD regardless of the cord lesion length and the presence of positive AQP4 antibody can occur in systemic autoimmune diseases.

**Keywords:** Neuromyelitis optica spectrum disorders, Autoimmune diseases, SLE, Sjogren's syndrome

## Background

Neuromyelitis optica spectrum disorders (NMOSD) are an immune-mediated neurological disorder, affects the central nervous system (CNS), especially the optic nerves and myelitis affecting a long segment of the spinal cord. The aquaporin-4 antibodies have a role in the autoimmune process, which emphasizes the role of humoral immunity in etiopathogenesis [1].

In recent years, clinical phenotypes have been described, involving different sites of the CNS alongside the optic nerves and spinal cord, leading to the introduction of the widely accepted term especially after associated with aquaporin-4 antibodies has been termed [2].

NMOSD is a relapsing condition. It has a characteristic magnetic resonance imaging (MRI) findings of longitudinally extensive transverse myelitis with optic neuritis; these clinical and radiological findings often suggestive for NMOSD [3].

Considering NMOSD as an autoimmune disease, several reports addressed the association with other systemic autoimmune diseases, organ-specific autoimmune disorders, malignancies, and infectious diseases [4]. Interestingly, the strong association between NMO and autoimmune disorders, such as systemic lupus erythematosus (SLE) or Sjogren's syndrome (SS), furthermore non-organ-specific autoantibodies (e.g., anti-nuclear antibody, extractable nuclear antigen) also has been detected [3, 5].

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It is well known that SLE and SS have several neurological complications [6–9], not only vasculitis related but also demyelinating inflammatory disorders such as transverse myelitis and NMOSD is still poorly understood. Several reports described transverse myelitis associated with only autoantibodies that were SLE or SS related. Moreover, those patients do not have a systemic manifestation of such diseases [10, 11]. These findings raised the debate, if NMOSD is being coexisting but separate diseases or a result of underlying autoimmune disease. Unfortunately, the autopsy studies of confirmed SLE and NMOSD cases failed to solve this debated question [12–15].

## Main text

### Methods

The current review was done using the search of related articles, case reports, case series, or meta-analysis on the PubMed database until 2019. We have searched with keywords including neuromyelitis optica spectrum disorders, including both seropositive and seronegative entities, Devic's disease, autoimmune diseases, SLE, Sjogren's disease, vasculitis, rheumatoid arthritis, systemic sclerosis, connective tissue diseases, scleroderma, sarcoidosis, antiphospholipid syndrome, and ankylosing spondylitis. We have included only all related articles published in English.

### Results of investigation

The international consensus diagnostic criteria for neuromyelitis optica spectrum disorders 2015 had stated diagnostic criteria to diagnose NMOSD (Figs. 1, 2, and 3) ruling out mimics is crucial in the new criteria including ischemic myelopathy which usually occurs less than 4 h, sarcoidosis or neoplasm usually progress more than 4 weeks, progressive deteriorating demyelination with the oligoclonal band or partial myelitis is characteristic for multiple sclerosis, anti-myelin oligodendrocyte glycoprotein (anti-MOG) with its specific clinical, radiological, and laboratory findings; also, HIV and syphilis can present with picture mimics NMOSD [16]. So, studying mimics, in particular, seronegative NMOSD mimics, which represent a difficult diagnostic challenge, is an important step in NMOSD consensus 2015 criteria. Exclusion of mimics with the absence of better explanation of clinical phenomenology, electrophysiological, and radiological archetypal is the basic principle for diagnosis of seronegative NMOSD in the domain of rheumatologic disorders [16–18].

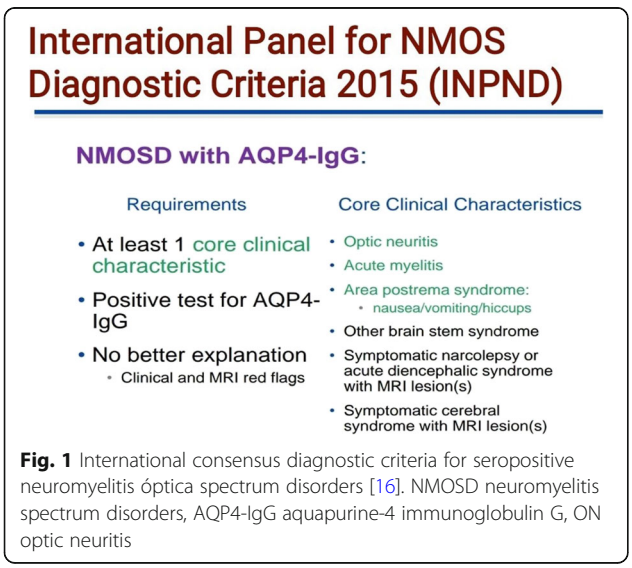


**Fig. 1** International consensus diagnostic criteria for seropositive neuromyelitis óptica spectrum disorders [16]. NMOSD neuromyelitis spectrum disorders, AQP4-IgG aquapurine-4 immunoglobulin G, ON optic neuritis

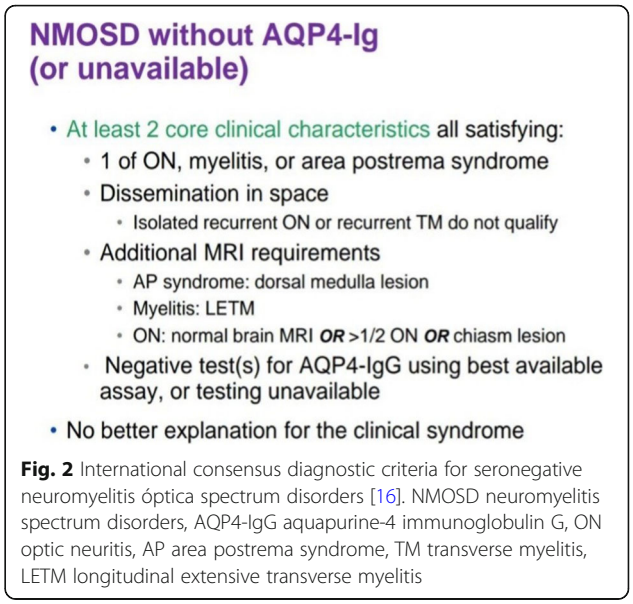


**Fig. 2** International consensus diagnostic criteria for seronegative neuromyelitis óptica spectrum disorders [16]. NMOSD neuromyelitis spectrum disorders, AQP4-IgG aquapurine-4 immunoglobulin G, ON optic neuritis, AP area postrema syndrome, TM transverse myelitis, LETM longitudinal extensive transverse myelitis

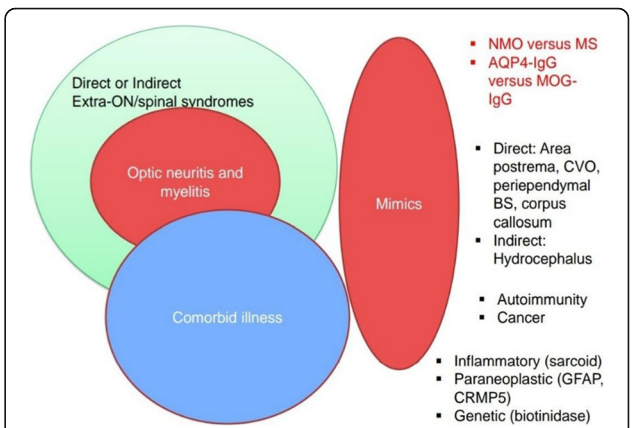


**Fig. 3** Mimics of neuromyelitis optica spectrum disorders [16]. AQP4-IgG aquapurine-4 immunoglobulin G, ON optic neuritis, CVO circum ventricular organ, BS brain stem, MS multiple sclerosis, NMO neuromyelitis optica, MOG-IgG myelin oligodendrocyte glycoprotein, GFAP glial fibrillary acidic protein, CRM5 collapsin response-mediator protein-5

### Spinal cord MRI

Spinal cord MRI usually presents with longitudinally extensive spinal cord lesions, extending for three or more vertebral segments on T2-weighted MRI, affecting the central cord gray matter on axial sections, associated with edema and gadolinium enhancement. Sixty percent affects the cervical cord and may extend into the medulla. The enhancement disappears with treatment and remissions [16]. On the other hand, longitudinally extensive transverse myelitis is unlikely to occur in adult patients with relapsing-remitting multiple sclerosis (RRMS). However, short-segment transverse myelitis, which could be presented in both MS and NMOSD, still represents challenges in differentiation despite different peripheral or central presentations in axial spinal MRI cuts, respectively [16, 17].

### MRI of the brain and orbits

MRI of the brain could be normal in 55 to 84% of patients at the time of presentation, rather than optic nerve gadolinium enhancement. However, MRI evidence of brain involvement develops over time in up to 85% of NMOSD patients as in central medulla, hypothalamus, area postrema, and diencephalon, corresponding to regions of high AQP4 expression, but is also found within subcortical white matter [16].

RRMS is differentiated from NMOSD by clinical, pathological, and laboratory findings. However, in seronegative NMOSD, the differentiation could be challenging. It was difficult to completely differentiate ON-NMOSD (optic neuritis related to neuromyelitis optica spectrum) from ON-MS (optic neuritis related to multiple sclerosis). ON-NMOSD patients tended to have simultaneous bilateral ON involvement, long-extensive posterior segment involvement extending to chiasma with visual field pattern, and poorer long-term visual outcome than individuals with ON-MS [16–18].

Additionally, evoked potential (EVP) assessment can help in such conditions. Recent studies had shown that NMOSD is usually associated with the absence of visual EVPs due to severe neuroaxonal loss after optic neuritis and, absence of motor EVPs in lower extremities; however, a delay in these potentials in more frequently with patients with RRMS, furthermore NMOSD did not present subclinical EVPs as RRMS did. None of the NMOSD patients had revealed abnormal auditory brainstem responses. EVPs can be considered as an investigation modality to differentiate NMOSD from RRMS [17, 18].

## Neuromyelitis optica and its association with systemic autoimmune diseases

Autoimmune diseases could be the cause of NMOSD; however, another hypothesis considers it as co-associated in a nonspecific way as optic neuritis and myelitis, can occur in some other diseases as paraneoplastic diseases and systemic autoimmune diseases [19, 20].

In the last two decades, some reported cases of a long segment of transverse myelitis (TM) and optic neuritis suggestive of NMOSD associated with Sjogren's syndrome or SLE [21]. In our PubMed search, most of the results were case reports, only eight observational studies were found, and most of the associations were related to SS and SLE (Table 1) [22–28, 30].

TM was long extensive transverse myelitis (LETM) in both SLE and SS with co-associated NMOSD [31].

Patients with systemic autoimmune disease who develop long segment transverse myelitis, associated with optic neuritis, confirmed with MRI lesion patterns even with negative aquaporin-4 antibody serology are very likely to have coexisting NMOSD. The aquaporin-4 autoantibodies test could be suppressed by the concomitant use of immunosuppressive medications and steroids chronically used for the autoimmune disease, increasing the percentage of a negative serological test for aquaporin-4 autoantibodies [32].

**Table 1** Comparison of studies of NMO clinical syndromes and systemic autoimmune rheumatic diseases

| Reference | Number of patients | Sex | Autoimmune disease | Age with NMO | NMO antibodies | Geographic district |
|---|---|---|---|---|---|---|
| Min et al. [22] | 9 | 9F | SS | NA | 5 +VE, 1 –VE, 3 NA | South Korea |
| Kim et al. [23] | 7 | 7F | SS | NA | 4 +VE, 1 borderline | South Korea |
| Kolfenbach et al. [24] | 6 | NA | SS | NA | 4 +VE, 2 –VE | USA |
| Estiasari et al. [25] | 9 | 8F | SS | 34.6 ± 12 | 7 +VE, 2 –VE | Japan |
| Katsumata et al. [26] | 6 | 6F | 3SS, 3SLE | 31.3 ± 12.98 | 1 +VE, 2 –VE; 1 +VE, 2 –VE | Japan |
| Qiao et al. [27] | 11 | 10F | SS | NA | 6 +VE, 1 negative, 4 NA | China |
| Qiao et al. [28] | 43 | 38F | SS, NMO before sicca, syndrome in 31 | 35.3 ± 12.2 | 25 +VE, 3 –VE, 5 NA | China |
| Salama et al. [29] | 20 | 17F | 2 RA/1SLE, 6 ANA positive, 1 anti DNA positive | 27.8 | 10 +VE | Egypt |
| Martín-Nares et al. [30] | 12 | 11F | 7SLE/5SS | 39 | 12 +VE* | Mexico |

*F* female, *B* brain, *NA* not available, *NMO* neuromyelitis optica, *SS* Sjogren's syndrome, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis
*Based on Martín-Nares et al., the 12 patients were included with positive NMO-antibody

### Systemic lupus erythematosus

SLE is a systemic inflammatory autoimmune disease. Neuropsychiatric SLE is one of the major organs affected in SLE [33]. One of the most common neuro-ophthalmologic SLE manifestations is optic neuropathy (ON) [34], and up to 1–2% of the patients develop TM with poor prognosis [35].

A literature review of Shahmohammadi et al. had reported nineteen SLE patients, their mean age was 30.39 ± 12.57, and 94.7% of them were females and reported to have SLE and NMOSD. A large percentage of patients (81.82%) had a positive AQP4 antibody test, and 73.7% diagnosed as SLE prior to the NMOSD presentation. However, TM was more frequently reported than ON [31].

In a recent systematic review of 104 SLE patients diagnosed with the demyelinating syndrome, 63 patients were classified as NMOSD with the characteristic LETM was the most common presentation. Most of the patients were females, and it had a worse prognosis compared to other demyelinating syndromes [36].

Another study on 626 admitted patients with active SLE or SS; six patients had clinical suspicion of NMOSD; two of them were having AQP4 antibody-positive, one SLE and one SS [26].

A recent single-center retrospective study in which they included patients with the diagnosis of NMOSD and AQP4-IgG seropositive and association with SLE and SS found that 12 patients fulfilled the inclusion criteria; 91.7% were females, and all patients were AQP4-IgG seropositive. Seven (58.3%) of them had SLE. In five (41.7%) patients NMOSD followed autoimmune onset, four (33.3%) patients had a simultaneous presentation. The mean age at the first neurological event was 39 years [30].

### Sjogren's syndrome

SS is an autoimmune disorder with whole mark manifestations of sicca syndrome secondary to salivary and lacrimal gland autoimmune lymphocytic infiltration [37]. Peripheral neuropathy is considered the most common neurologic manifestation [38]. Although other CNS involvements as transverse myelitis (TM) and optic neuritis are less common, however, it is still one of the reported complications [39, 40]. Recently, there are increasing reports of patients with SS with NMOSD manifestations and were seropositive for AQP4 antibodies, and other cases fulfilled the clinical and radiological NMOSD criteria and seronegative for AQP4 antibodies [26, 30].

Up to 116 SS reported patients presented with NMOSD. Most of them were females [31]. It has been reported in the pediatric age group as well [41, 42]. It was seropositive in 83.72% of 86 patients who were tested for AQP4 antibodies [31].

SS had a severe progressive NMOSD course in comparison to patients without SS [27, 43]. Furthermore, brain involvement was reported more frequently in patients with SS compared to SLE, especially cortical blindness and encephalopathy [44], apraxia, and aphasia [45] with positive serum AQP4 antibodies. In a retrospective study conducted on Chinese patients, 43 out of 616 patients had been diagnosed by NMOSD, 89.3% of the primary SS patients with NMOSD were seropositive to AQP4 antibodies, as well as 88.9% were CSF positive for AQP4 antibodies. Primary SS associated NMOSD patients were AQP4 antibody seropositive [28]; another recent study had reported 12 patients retrospectively with seropositive NMOSD associated with SLE and SS, five (41.7%) were SS, and in three (25%) NMOSD preceded SS onset [30].

### Other systemic autoimmune diseases

The coexistence of NMOSD with other autoimmune rheumatologic disorders has been reported, [46] as in sarcoidosis [47], rheumatoid arthritis [48], ankylosing spondylitis [44], antiphospholipid syndrome (APS) [49, 50], and systemic sclerosis [51–53].

Jarius et al. studied 109 Caucasian patients with neurological manifestations secondary to connective tissue diseases; 40 patients were having NMOSD (recurrent optic neuritis NMO and LETM); of them, 78% were AQP4 antibody seropositive [54].

### Subclinical NMOSD with only positive autoantibodies of rheumatic disease:

Concomitant association of organ and non-organ specific autoantibodies have been reported in NMOSD patients [22], such as APS antibodies [55, 56], anti-RO/SSA and LA/SSB [55, 57], anti-nuclear antibody (ANA) [55, 58, 59], double-stranded DNA antibodies, anti-centromere antibodies, anti-Scl70 antibodies, anti-histone antibodies, anti-smooth muscle antibodies, rheumatoid factor, pANCA, and cANCA of unknown specificity [55] been variably reported without any evidence of clinical disease. Among these autoantibodies, Anti-RO/SSA and ANA are the most common in a patient with NMOSD [48, 60]. Association of ANA with AQP4 seropositive increases the sensitivity without reducing the specificity of NMOSD diagnosis [60]. However, the seronegative pattern had been documented with autoimmune diseases [27, 28]. The association of these antibodies changes the prognosis or diagnosis is still controversial.

### Pattern of NMOSD in the Egyptian population

In a recent interesting study to describe the pattern of NMOSD in Egyptian population, the disease onset tends to be in younger age group, 50% were AQP4

seropositive, interestingly concomitant autoimmune diseases were observed in two patients with rheumatoid arthritis, one with lupus, two with hypothyroidism, and one with myasthenia gravis. Moreover, three other patients had a family history of autoimmune disorders. Not only the associated immunologic disorder had been observed, but also positive ANA test was found in 6 patients, two of them also had seropositive for the AQP4 antibody, and anti-ds-DNA was the only weak positive result in one patient [29].

## Mechanisms of co-association of NMOSD with systemic rheumatic autoimmune disease

Notably, there is no accurate data about the prevalence and incidence of NMOSD and rheumatic autoimmune disease. Based on limited case reports and small numbers of case-control studies, SS and SLE are the most commonly reported to be associated with NMOSD. It is more common to affect the middle age group and reported mostly in females. Autoimmune diseases can cause neurological manifestations as same as NMOSD; with positive antibody, the diagnosis of NMOSD is definite. However, it is a challenging diagnosis with the seronegative disease with typical clinical and radiological NMOSD, although NMOSD should also be considered in typical cases with undetectable antibodies. The sensitivity and specificity of AQP4 antibodies in idiopathic NMOSD patients and in association with autoimmune diseases are similar, illustrating that both are distinct diseases, and it is an association rather than the same etiology [27, 28, 55, 61].

Co-association could be related to genetic factors that predispose to autoimmunity; the etiopathogenesis of NMOSD with autoimmune diseases has not been fully understood; however, both are antibody-mediated disorders, and variety of antigen presentation by HLA in different ethnicity can raise the incidence and prevalence of autoimmunity in some races. NMOSD and its coexistence with SS have been recorded higher in non-Caucasian populations [50, 61].

Not only does NMOSD associate with long segment TM but also, it has been reported with short segment TM with positive AQP4 antibodies associated with systemic autoimmune disease [62, 63].

NMOSD associated with autoimmune diseases is considered more severe with poor prognosis. It could be related to vasculopathy and vasculitis due to rheumatic autoimmune diseases that could facilitate the occurrence of NMOSD by disrupting the blood-brain barrier and facilitate the entrance of the AQP4 antibody to CNS [64].

The pathology detected in NMOSD has many common characters in different CNS-studied tissues with perivascular immunoglobulin and complement deposition, and transmural vasculitis is absent; however, till now, there are no specific pathological features associated with SLE cerebritis that characterize brain lesions in NMOSD. The pathologic role of aquaporin-4-specific antibodies had been established in vitro and in vivo experimental studies [65, 66].

Evidence of salivary glands inflammation was found in NMOSD patients without clinical SS [67]. It is possible that the common epitopes between AQP5 in salivary glands and AQP4 in CNS may explain the association between NMOSD and SS [68]. From our point of view, the common idea of epitope spreading could explain the co-association and join between the idea of genetic autoimmune susceptibility and even the idea of the blood-brain barrier disruption with antigen sequestration.

There is no current evidence for drug superiority in the case of NMOSD associated with autoimmune diseases; although with the humoral B cell-related disease, rituximab is considered one of the best options, especially with seropositive pattern [69, 70].

In rheumatologic diseases, cyclophosphamide and methotrexate are commonly employed therapies that may also favorably influence the course of concomitant NMOSD. Rheumatologists and neurologists should avoid monoclonal antibody or fusion protein therapies that interfere with tumor necrosis factor-alpha function, including such as infliximab, adalimumab, or etanercept (each is approved for rheumatoid arthritis, spondyloarthropathies, including psoriatic arthritis, among other indications) because they have been associated with CNS demyelinating events, although we do not know their specific effects on NMOSD [21, 32].

### Prevention of relapse and highly suggestive symptoms

Induction of remission is usually achieved by high-dose pulse methylprednisolone for 3–5 successive days. Long-term immunosuppression treatment is recommended initiation for the prevention of attacks as soon as the diagnosis of NMOSD is established [70–73]. However, the treatment duration is yet to be determined. The systemic immunosuppression first-line monotherapy treatments that can be used for NMOSD are azathioprine, rituximab, and mycophenolate mofetil; although there is a lack of the comparative data, treatment with all these agents associated with a significant decrease in annual relapse rates ranging [73–75]. Immunosuppression is continued usually for at least 5 years in AQP4 seropositive patients, even those presenting with a single attack, to limit the high risk for relapse. Some experts suggest that life-long therapy is appropriate, given the often devastating nature of the disease. Others suggest that the duration of immunosuppression should be determined according to the severity of attacks and disability [76, 77].

## Conclusions

In view of the above data, NMOSD could be associated with a variety of autoimmune disorders, most commonly reported to be co-associated with SLE and Sjogren's syndrome; on the other hand, positive autoantibodies of rheumatic autoimmune diseases can be detected in patients with NMOSD without systemic manifestation. The early clinical diagnosis of NMOSD can be appreciated in systemic autoimmune diseases regardless of the cord lesion length and the presence of positive AQP4 antibody primarily if the patient is receiving any immunosuppressive affecting humoral immunity.

The pathogenesis of co-association is still unclear. Further studies are needed to address the co-association in relation to genetic studies, racial distribution, biomarkers, severity, and treatment response.

### Abbreviations

NMOSD: Neuromyelitis optica spectrum disorders; AQP4: Aquaporin-4; SLE: Systemic lupus erythematosus; SS: Sjogren's syndrome; NMO: Neuromyelitis optica; CNS: Central nervous system; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; EVPs: Evoked potentials; TM: Transverse myelitis; LETM: Long extensive transverse myelitis; APS: Antiphospholipid syndrome; ANA: Anti-nuclear antibody; AQP4-IgG: Aquapurine-4 immunoglobulin G; AP: Area postrema syndrome; ON: Optic neuritis; CVO: Circum ventricular organ; BS: Brain stem; MS: Multiple sclerosis; MOG-IgG: Myelin oligodendrocyte glycoprotein; GFAP: Glial fibrillary acidic protein; CRM5: Collapsin response-mediator protein-5

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### Authors' contributions

All authors have read and approved the manuscript. BE: main idea, authoring; SH: collect references, figures; TE: editing radiology-related sections; and SG: editing and supervision.

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### Competing interests

The authors declare that there is no conflict of interest.

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