CENTRAL VEIN SIGN FOR DIFFERENTIAL DIAGNOSIS OF DEMYELINATING DISEASES OF CNS

Belov SE[1,2], Gubsky IL[2], Lelyuk VG[2], Boyko AN[1,2] ✉

[1] Pirogov Russian National Research Medical University, Moscow, Russia

[2] Federal Center of Brain Research and Neurotechnologies of FMBA, Moscow, Russia

The search for highly sensitive and highly specific biomarkers of MS, including neuroimaging biomarkers, continues. One of such biomarkers is the central vein sign detectable on SW and T2-weighted MR images. The sensitivity and specificity of methods used for central vein sign detection vary. This article describes two clinical cases of patients with similar neurological symptoms which required making differential diagnosis between multiple sclerosis and secondary demyelination in the presence of a systemic disorder (systemic lupus erythematosus). In addition to routine MR sequences, we used SWI generated by a 3T scanner. The lesions with the central vein sign were counted; the proportion of perivenular lesions was determined. In the multiple sclerosis case, all the lesions were perivenular; the proportion of lesions with the central vein sign in the patient with secondary demyelination in the presence of systemic lupus erythematosus was 16.7%. The use of SW images improved the informative value of the analysis.

Keywords: central vein sign, differential diagnosis, multiple sclerosis, demyelinating disease, CNS, secondary demyelination, MRI, SWI, SWAN

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Compliance with ethical standards: informed consent was obtained from both patients.

✉ **Correspondence should be addressed:** Alexey N. Boyko
Ostrovityanova, 1, 117437, Москва; boykoan13@gmail.com

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ИСПОЛЬЗОВАНИЕ СИМПТОМА ЦЕНТРАЛЬНОЙ ВЕНЫ ДЛЯ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ ДЕМИЕЛИНИЗИРУЮЩИХ ЗАБОЛЕВАНИЙ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

С. Е. Белов[1,2], И. Л. Губский[2], В. Г. Лелюк[2], А. Н. Бойко[1,2] ✉

[1] Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия

[2] Федеральный центр мозга и нейротехнологий Федерального медико-биологического агентства, Москва, Россия

Продолжается поиск биомаркеров, в том числе выявляемых с помощью методов нейровизуализации, обладающих высокой чувствительностью и специфичностью в диагностике РС. В качестве одного из них можно рассматривать симптом центральный вены, выявляемый при МРТ с использованием импульсной последовательности SWI и T2*-взвешенных изображений. В то же время различаются данные по специфичности и чувствительности различных методов для выявления этого синдрома. Представлено два случая, близких по неврологическим нарушениям, требующих дифференциальной диагностики между РС и вторичной демиелинизацией на фоне системного заболевания (системной красной волчанки). Помимо рутинных МРТ-последовательностей, использовали SWI на томографе с индукцией магнитного поля 3 Тл. Подсчитывали очаги с симптомом центральной вены с определением доли перивенулярного поражения. В случае РС все рассматриваемые феномены локализовались перивенулярно, при вторичной демиелинизации на фоне системной красной волчанки доля очагов с симптомом центральной вены составила 16,7%. Последовательность SWI повышала информативность анализа.

Ключевые слова: симптом центральной вены, дифференциальная диагностика, рассеянный склероз, демиелинизирующее заболевание, ЦНС, вторичная демиелинизация, МРТ, SWI, SWAN

Вклад авторов: С. Е. Белов — анализ литературы, участие в разработке дизайна исследования, подбор пациентов, оценка клинических показателей, написание статьи; И. Л. Губский — участие в разработке дизайна исследования, получение и анализ данных МРТ, написание статьи; В. Г. Лелюк — участие в разработке дизайна исследования, анализ результатов МРТ, участие в написании статьи; А. Н. Бойко — участие в разработке дизайна исследования, подбор пациентов, оценка клинических показателей, написание статьи.

Соблюдение этических стандартов: все пациенты подписали добровольное информированное согласие на участие в исследовании.

✉ **Для корреспонденции:** Алексей Николаевич Бойко
ул. Островитянова, д. 1, 117437, г. Москва; boykoan13@gmail.com

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As new disease-modifying treatments (DMTs) for multiple sclerosis (MS) are being developed and introduced into clinical practice, and our knowledge about the pathogenesis and molecular underpinnings of this condition is expanding, adequate diagnostic criteria and procedures are becoming increasingly important. MS requires expensive long-term treatment; therefore, the diagnosis must be timely and accurate. The key 2017 McDonald criteria for MS [1] are: clinical and MRI evidence of dissemination of demyelinating lesions in time and space, exclusion of other disorders, and the presence of oligoclonal bands in the cerebrospinal fluid (CSF). However, despite the guidance provided by the McDonald criteria, diagnostic errors are not uncommon, partly due to the absence of MS-specific MRI features and biochemical/immunological markers [2, 3]. This drives the search for specific MS biomarkers, one of which might be the central vein sign.

The central vein sign can be visualized on SWI (susceptibility-weighted imaging) and T2-weighted gradient-echo sequences. SWI is sensitive to paramagnetic, supermagnetic and ferromagnetic compounds like deoxyhemoglobin and iron and is capable of detecting local changes to the magnetic field [4]. The central vein sign shows on the SW-images of patients with progressive demyelination in the central nervous system (CNS) as a blood vessel inside a white matter lesion that appears as

a hypointensity due to the presence of deoxyhemoglobin in the vein. An area of autoimmune inflammation and demyelination (a plaque) forms around the vein [5, 6].

After a 2008 publication by Tallantyre et al., a series of reports demonstrated that the central vein sign was a sensitive diagnostic marker for MS and could be used to differentiate MS from other demyelinating diseases. Although those publications were scarce and the sample sizes were small, they showed the potential of the central vein sign as an MS biomarker [7–17]. In those studies, the proportion of lesions with the central vein sign was calculated and a threshold for reliable differentiation between MS and MS-resembling conditions was determined. The established threshold frequency of perivenular lesions that could be used to differentiate between MS and other demyelinating diseases of the CNS with high sensitivity and specificity was 40–50%. This article reports 2 clinical cases in which SWI, in addition to routine MRI sequences, was used to look for the central vein sign.

Description of clinical cases

Patients whose clinical cases are presented below underwent standard diagnostic tests for MS: physical examination, neurological assessment with EDSS (Expanded Disability Status Scale), lumbar puncture with CSF and serum analysis for the presence of oligoclonal bands, contrast-enhanced MRI with sequences routinely used in MS diagnosis, and SWI for central vein sign detection.

We used a 3T Discovery 750w scanner (General Electric; USA). In GE scanners, susceptibility-weighted imaging is called SWAN and has the following parameters: FOV (field of view) 22 cm; number of slices 178; TE (echo time) 28 ms; TR (repetition time) 47 ms; flip angle 8°; number of echoes 6; slice thickness 0.8 mm [18].

The clinical evaluation of the central vein sign was carried out using the criteria of the North American Imaging in Multiple Sclerosis Cooperative [19].

On MR images, the central vein sign has the following radiographic features:

1) it looks like a thin hypointense line or a small hypointense dot;

2) it can be visualized in at least 2 planes and appears as a thin line in at least one plane;

3) its diameter is under 2 mm;

4) it courses, partially or fully, through the lesion;

5) it is located in the center of the lesion at equal distances from its edges and passes through the edge at no more than 2 sites, regardless of the lesion's shape.

Exclusion criteria for lesions: diameter over 3 mm; confluent lesions; lesions with several different blood vessels inside; poorly visualized lesion.

Case 1

A 32-year-old female patient presented with complaints of numbness in her right arm, a burning sensation on the left side of the body and in her left extremities; the symptoms had started a month before the appointment. A contrast-enhanced brain MRI scan revealed multiple, possibly demyelinating MS lesions in the white brain matter, with contrast uptake in one of the lesions. The acquired MR images showed lesions of different age, with and without contrast uptake. A few days later, the patient developed tenderness to touch and a sensory disturbance (dysesthesia) on the left side of the body and in her left extremities. The patient was prescribed pulse therapy with 5 g methylprednisolone, which slightly improved her condition. She was hospitalized to a neurology unit to undergo further tests and treatment. The patient had a history of chronic hypothyroidism and was on 50 μg L-thyroxine. Antibodies (IgG+IgA+IgM) to aquaporin-4 < 1:10 (which was within the reference range of < 1:10); oligoclonal IgG in CSF/serum as of April 14, 2021: type 2 synthesis typical for autoimmune processes in the CNS. The visual evoked potential test conducted on April 14, 2021 revealed no pathology of the visual system.

On examination the patient's condition was satisfactory. Her posture was active, and she was fully conscious. Height: 172 cm; weight: 58 kg; body type: normosthenic. Respiratory rate: 18 breaths per minute; heart rate: 68 beats per minute. Blood pressure: 110/70 mmHg. No pain on kidney percussion on both sides. The patient denied dysuria or fecal incontinence and reported regular bowel movements.

Neurological assessment. The patient was fully conscious and did not have any speech impairments. She was calm, cooperative, well-oriented in time and space, and knew her personal identity. No symptoms of non-focal brain or meningeal damage were detected. Cranial nerve (CN) I (*n. olfactorius*): sense of smell not impaired; CN II (*n. opticus*): acuity and visual fields not impaired; CN III (*n. oculomotorius*), IV (*n. trochlearis*), and VI (*n. abducens*): full range of eye movement preserved, palpebral fissures unremarkable, D = S. Pupils: OD = OS, round, pupil size was normal for the used lighting conditions, direct and consensual pupillary reflexes were intact. CN V (*n. trigeminus*): corneal reflexes preserved; no altered sensations in the face. The strength and function of mastication muscles were preserved. CN VII (*n. facialis*): the face was symmetrical; sense of taste preserved on the anterior two-thirds of the tongue. CN VIII (*n. vestibulocohlearis*): no hearing loss or nystagmus detected. CN IX (*n. glossopharingeus*), X (*n. vagus*), and XI (*n. accessorius*): gag reflex preserved, D = S. No uvular deviation detected. No dysphonia, dysarthria or dysphagia. Head posture was unremarkable; the full range of motion was preserved for the head and the muscles of the upper chest and shoulders. CN XII (*n. hypoglossus*): no signs of tongue deviation. No changes in muscle tone. No paresis. Exaggerated deep tendon reflexes: S ≤ D. Abdominal reflexes were absent. The Babinski reflex was absent bilaterally. Abnormal superficial sensations were detected in the left extremities. Vibratory sense was normal. The Lasegue, Neri, Wasserman, and Matskevich tests were negative, indicating the absence of tension in the peripheral nerves. The patient had S-shaped thoracolumbar scoliosis, with a right arc. The right shoulder blade was prominent. The patient was a bit unsteady during the Romberg test; her performance during coordination tests was satisfactory. The patient denied any pelvic floor dysfunction. Her EDSS score was 2.0, suggesting moderate disability.

Brain, cervical and thoracic spine MRI conducted on April 23, 2021 was suggestive of possibly demyelinating supra- and infratentorial lesions in the white brain matter (MRI findings were consistent with dissemination in time and space). The total number of supratentorial lesions on SW and FLAIR images was 6. Of them, 4 were suitable for the analysis. The central vein sign was detected in all of those 4 lesions. Other 2 lesions could not be used for the analysis because of their size (< 3 mm); interestingly, the central vein sign was detected in one of those two lesions (Fig. 1)

Case 2

A 42-year-old female patient was hospitalized in March, 2021. Presenting complaints: malaise, easy fatigability, headaches,

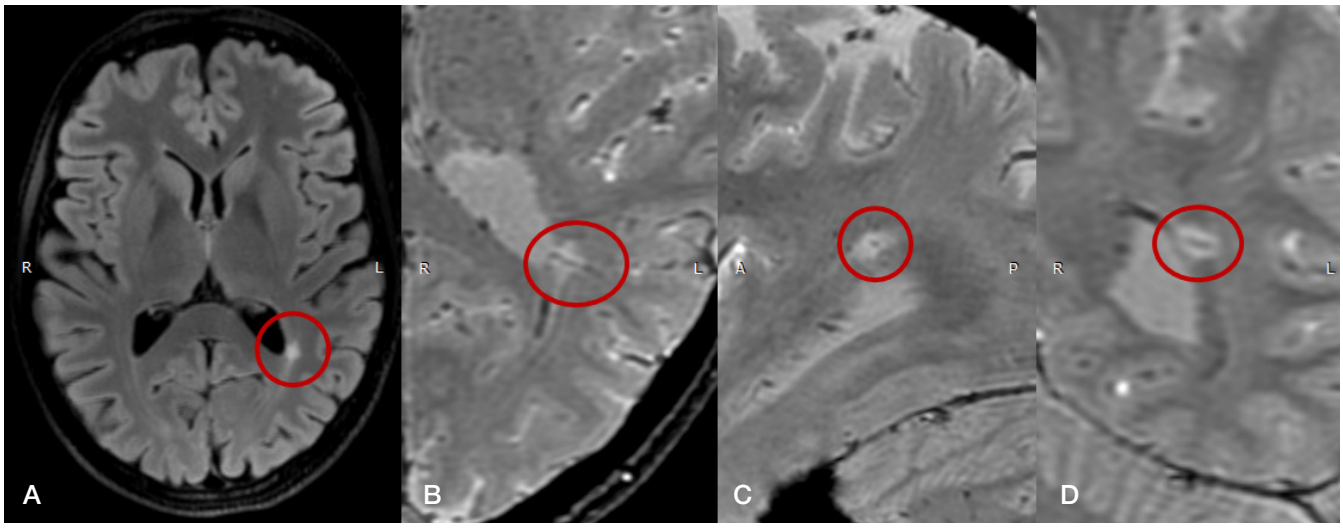

Fig. 1. Magnetic resonance images of patient 1. **A**. A T2-weighted fluid-attenuated inversion recovery (FLAIR) image, the axial plane. The image shows a periventricular lesion in the posterior horn of the left lateral ventricle (marked by the *red* oval). **B**. A susceptibility-weighted (SW) image, the axial plane. The image shows a central vein sign in the lesion near the posterior horn of the left ventricle (marked by the *red* oval). **C**. A susceptibility-weighted (SW) image; the sagittal plane, the central vein sign appears as a dot in the lesion (marked by the *red* oval). **D**. A susceptibility-weighted (SW) image, the coronal plane; the central vein sign appears as a thin line in the same lesion (marked by the *red* oval)

dizziness, limb numbness, migratory pain affecting the entire body, blurred vision, blind spots, weakness in the left leg during walking, episodes of urinary incontinence.

Past history: in August 2017, the patient had an attack of rotatory vertigo with nausea and vomiting, which lasted for 6–8 h. The patient was recommended to take betahistine. The second attack occurred in November and was also accompanied by nausea and vomiting. The patient was hospitalized but discharged home soon without a verified diagnosis. Her condition worsened in May 2018. Symptoms of non-focal brain damage (dizziness) were deteriorating, and vision loss was progressing. The patient developed numbness in the limbs, pain in the spine and joints, and overall was feeling weak. She developed painless mouth ulcers and was losing hair. A malar (butterfly-shaped) rash appeared on her cheeks and nose. The medical history reported increased photosensitivity of the skin. The patient underwent pulse therapy with methylprednisolone, which had a beneficial effect. Immunomodulatory drugs were not prescribed. In 2018, the patient underwent lumber puncture; the analysis of CSF/serum for oligoclonal IgG suggested type 3 synthesis. AT to aquaporin-4 were not detected. MOG antibody test (March 11, 2019): 10.5 pg/ml (the reference range: 0–15 pg/ml). The patient was hospitalized to undergo further tests and receive treatment.

On physical examination the patient's condition was satisfactory. Her posture was active. Height: 165 cm; weight: 55 kg; body temperature: 36.8 °C. A butterfly-shaped malar rash was visible on the patient's cheeks and nose. Heart rate: 16 beats per minute. Blood pressure: 120/70 mmHg. The patient denied any urinary or digestive disorders.

Neurological assessment: the patient was fully conscious, cooperative, well-oriented in time and space and knew her personal identity. She had complaints of vertigo. No symptoms of meningeal damage were detected. CN I (*n. olphactorius*): sense of smell not impaired. CN II (*n. opticus*): progressive loss of vision, blind spots; visual hallucinations not detected; no changes to color perception. CN III (*n. oculomotorius*), IV (*n. trochlearis*), and VI (*n. abducens*): full range of eye movement preserved. No signs of ptosis. Pupils: OD = OS; direct and consensual pupillary reflexes were intact;

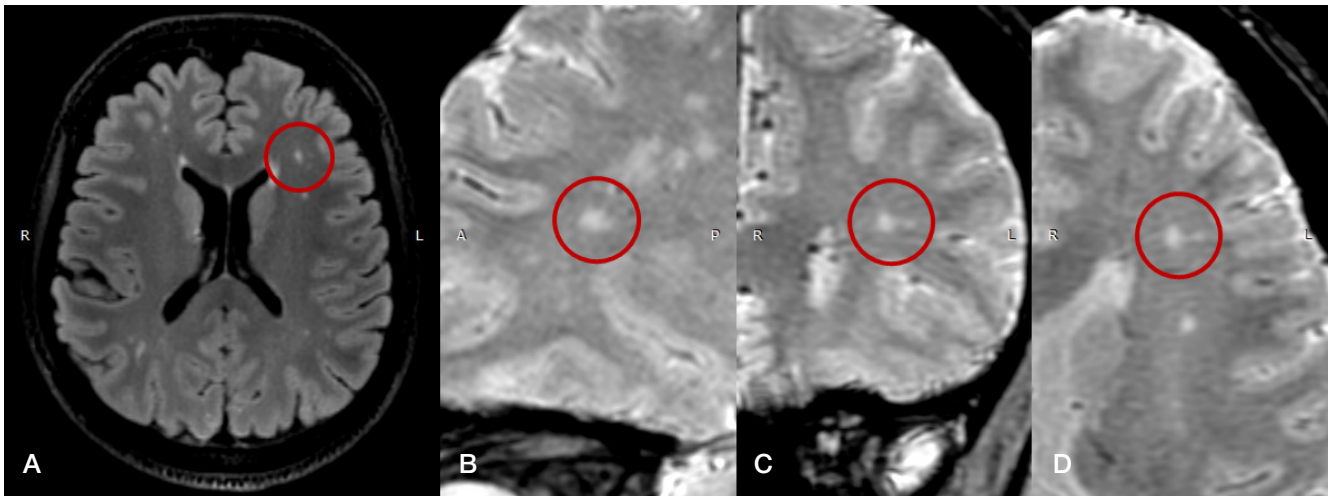

Fig. 2. Magnetic resonance images of patient 2. **A**. A T2-weighted fluid-attenuated inversion recovery (FLAIR) image, the axial plane. The image shows a round lesion in the deep white matter of the left frontal lobe (marked by the *red* oval). **B.** A susceptibility-weighted (SW) image, the axial plane. The image shows the same lesion, the central vein sign is not visualized (the *red* oval). **C**. A susceptibility-weighted (SW) image, the sagittal plane. The same lesion, the central vein sign is not visualized; a smaller lesion not suitable for the analysis is located in close proximity (the *red* oval). **D**. A susceptibility-weighted (SW) image, the coronal plane. The same lesion, the central vein sign is not visualized (the *red* oval)

accommodation and convergence were normal. CN V (*n. trigeminus*): corneal reflexes were intact; no altered sensations in the face. The strength and function of mastication muscles were preserved. CN VII (*n. facialis*): no facial asymmetry at rest or during tests; the range of facial movements was fully preserved. No tearing, dry eyes or sensory impairment on the anterior two-thirds of the tongue were detected. CN VIII (*n. vestibulocohlearis*): no signs of hearing loss, noise or ringing sensation in the ears. CN IX (*n. glossopharingeus*): soft palate paresis not detected; the gag reflex was intact. No uvular deviation. CN X (*n. vagus*): the patient was able to swallow and showed no signs of dysphagia or dysphonia. CN XI (*n. accessorius*): head posture was unremarkable; the full range of motion was preserved for the head and the muscles of the upper chest and shoulders. CN XII (*n. hypoglossus*): the tongue was not deviated, without atrophy or fasciculations. Motor system assessment: muscle strength was not reduced, but muscle tone was decreased. Exaggerated tendon reflexes with extended reflexogenic zones; D = S. The Babinski reflex was absent bilaterally. No fasciculation or fibrillation was observed. No synkinesis, hyperkinesia or tremor were detected. Sensory system assessment: the patient had "conductive" hypoesthesia in her right limbs. The Lasegue and Neri tests were negative, indicating the absence of tension in the peripheral nerves. Coordination: slight staggering during the Romberg test due to non-vestibular causes; slight bilateral intention tremor during coordination tests. No gait disturbances were detected.

Brain, cervical and thoracic spine MRI conducted on March 3, 2021 showed multiple nonspecific (possibly, autoimmune) supratentorial lesions in the white matter that did not meet the criteria of dissemination in time and space. No contrast enhancement of the lesions was observed immediately and 15 minutes after contrast agent administration. The total number of supratentorial lesions on SW and FLAIR images was about 40. Precise counting was impossible due to the small size of the lesions and their confluence. Of all the lesions, 6 were suitable for the analysis; the rest were too small (< 3 mm). Of those 6 lesions, the central vein sign was observed in only one (16.7%) (Fig. 2).

Discussion

Case 1

The proportion of lesions with the central vein sign was 100%. Considering that the patient had typical clinical signs of MS and that the 2017 McDonald criteria were fulfilled, the final diagnosis was relapsing-remitting multiple sclerosis [1].

Case 2

Given type 3 intrathecal IgG synthesis, the absence of AT to aquaporin-4 and the absence of MRI features of MS (the 2017 McDonald criteria [1]), there was no evidence of a primary demyelinating disease. The patient's condition was consistent with a systemic autoimmune disorder (4 criteria of 11): a facial rash, increased photosensitivity, elevated antinuclear antibodies (1:640), and a past history of painless mouth ulcers and arthritis. The final diagnosis was undifferentiated systemic connective tissue disorder, possibly systemic lupus erythematosus, complicated by a secondary demyelination disorder of the CNS.

CONCLUSION

The clinical cases described in the article demonstrate the feasibility of using the central vein sign for the differential diagnosis of MS. Although the presented cases are quite typical and did not pose real difficulty in making the accurate diagnosis, SWI may be helpful in differentiating between primary and secondary demyelination. The meta-analyses of yet scarce studies investigating the diagnostic significance of the central vein sign for the differential diagnosis of MS and MS-resembling conditions (cerebral small vessel disease, secondary demyelination in the presence of rheumatic diseases, neuromyelitis optica) show that the central vein sign has 97% sensitivity and 99% specificity as an MS marker if the proportion of lesions with the central vein sign is over 45% [15, 17–19]. However, the frequency of this sign and the approaches to its analysis in various diseases need to be studied further because the reported sample sizes were small and the analyzed range of diseases that need to be differentiated from MS is quite narrow [20].

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