Susac syndrome: The effectiveness of Rituximab monotherapy

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Susac syndrome (SS) or retino-cochleo-cerebral vasculopathy is an extremely rare, severe, and potentially disabling condition. Underlying occlusive microangiopathy in SS is clinically characterized by the triad of encephalopathy, sensorineural hearing loss and branch retinal arterial occlusion. SS therapy envisages simultaneous use of high doses of glucocorticoids, intravenous immunoglobulins, cytostatics and Rituximab (RTX). This article presents a case of remitting-relapsing slow-progressive SS with typical clinical manifestations demonstrating successful treatment SS with RTX monotherapy; it also discuss the focus of RTX monotherapy should be targeted at SS cases with contraindications for glucocorticoids and cytostatics use, slow-progressive SS or at early stages.
Key words: Susac syndrome, retino-cochleo-cerebral vasculopathy, central nervous system vasculitis, rituximab
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СИНДРОМ СУСАКА: ЭФФЕКТИВНОСТЬ МОНОТЕРАПИИ РИТУКСИМАБОМ

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Синдром Сусака (СС), или ретикуло-кохлео-церебральньная васкулопатия, является крайне редким тяжелым инвалидизирующим заболеванием, в основе которого предполагают окклюзирующую микроангиопатию. Для СС характерна клиническая триада, включающая энцефалопатию, нейросенсорную тугоухость и окклюзию артерий сетчатки. Лечение СС недостаточно разработано; используют высокие дозы глюкокортикоидов, внутривенный человеческий иммуноглобулин циклофосфан и анти-В-клеточную терапию ритуксимабом (РТМ). Представлено описание случая СС с типичными клиническими проявлениями и волнообразным, медленно прогрессирующим течением заболевания, при котором отмечена эффективность монотерапии РТМ. Обсуждается целесообразность использования монотерапии РТМ на ранних стадиях СС, в случаях медленно прогрессирующего течения заболевания, при наличии противопоказаний для применения глюкокортикоидов и цитостатиков.
Ключевые слова: синдром Сусака, ретино-кохлео-церебральная васкулопатия, васкулит центральной нервной системы, ритуксимаб, внутривенный иммуноглобулин
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Retino-cochleo-cerebral vasculopathy (or Susac syndrome, SS) was first reported in the medical literature in 1979 by Dr. John Susac and co-authors [1]. It has also been referred to as "retinopathy, encephalopathy, deafness associated microangiopathy" (RED-M) or "small infarctions of cochlear, retinal and encephalic tissue" (SICRET). It could be under-diagnosed cases of so-called "seronegative" systemic lupus erythematosus.

SS is an extremely rare, severe, and potentially disabling condition, characterized by microangiopathy of autoimmune origin leading to occlusive endotheliopathy in the capillaries and precapillaries of the brain, inner ear and the retina [2, 3]. SS should be viewed as microangiopathy, not vasculitis due to absence of any signs of necrosis. Endotheliopathy leads to narrowing and occlusion of arterioles, followed by microinfarctions causing damage to axons, neurons and myelin of the brain white matter [3]. Morphological changes in the brain are characterized by focal microangiopathy, gliosis and inflammatory response with predominant recruitment of lymphocytes. Laboratory indicators of concurrent inflammation are not typical for SS.

The clinical picture of the SS is characterized by a triad of signs associated with damage to the brain, retina and auditory nerve commonly found in 85% of cases. However, at the onset this typical for SS clinical triad is present in less than 20% of patients, and most often only one out of three components will be found during the manifest phase of the disease [4–6], significantly complicating timely diagnosis of SS. The age at disease onset varies between 20 and 40 years, and SS is 1.5–3 times more common in women than in men [2, 6]. However, according to accumulated evidence, SS course is more severe and manifesting all features of clinical triad more often in men than in women [6].

Retinal damage leads to visual loss, although rare cases can be asymptomatic when only peripheral retina is involved. SS-associated encephalopathy can manifest with severe (sometimes migraine-like) headaches, or impaired concentration, memory weakening, depression or aggressive behavior. Auditory nerve involvement is associated with hearing loss, tinnitus, nystagmus, dizziness, which in turn can accelerate progression of mental disorders.

SS usually runs a monophasic course although some individuals can experience a polyphasic remitting-relapsing course with fluctuating level of symptoms for 1–2 years [3, 4–6]. In some

cases, SS symptoms eventually subside within a few years without any treatment. Four degrees of SS severity, from mild to extremely severe describe varying severity of clinical manifestations of encephalopathy and brain lesions detected with magnetic resonance imaging (MRI) [7].

Aggressive therapy with immunosuppressants (ultra-high doses of glucocorticoids (GCs) and cytostatics) in combination with intravenous immunoglobulins (IVIGs) and biological drugs, primarily rituximab (RTX) [7] are the mainstay of SS therapy, with intensity of treatment regimens depending on SS severity measured by severity of central nervous system (CNS) involvement.

The following clinical case illustrates a remitting-relapsing, slow-progressive SS with typical clinical manifestations, responding to RTX monotherapy.

Case report

Patient is a 37-year old female. She experienced her first episode of eye floaters in 2006, which resolved spontaneously. Funduscopic examination revealed edema of the fundus, and perivascular cuffing leading to diagnosis of retinal vasculitis. Such short-term visual impairment attacks recurred several times during 2006. There were no exacerbations of visual symptoms after the first pregnancy in 2007, but after the second in 2011 the patient noticed gradual shrinking of visual fields in the left eye. In 2013 and 2015 the patient gave births to her third and fourth child. Further progression of visual field loss was documented within a few months after the last birth. Although, no signs of disrupted visual sensory input either on the peripheral or central levels were found. Visual field defects also appeared on the right eye. Brain MRI revealed multiple focal lesions in the callosal body (Fig. 1) resembling a "snow-ball" on T2-weighted images (WI).

Recurrent headaches and hearing loss followed shortly afterwards. Audiogram revealed abnormal perception of medium and low frequencies in the right ear (Fig. 2). Second brain MRI showed new emerging focal lesions in the white matter. Meanwhile lab test failed to reveal whatever signs of inflammation in the blood or any abnormalities in the urine. A panel of immunological tests including antibodies to aquaporin-4 IgG and IgM, antineutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-deoxyribonucleic acid, cardiolipins and β2-glycoproteins antibodies also showed only negative results. Absence of oligoclonal IgG in the cerebrospinal fluid or whatever abnormalities in visual and auditory evoked potentials allowed to rule out the diagnosis of multiple sclerosis. Fluorescent angiography of the ocular fundus revealed the pattern of retinal angiitis, including uneven filling of the left upper-nasal arteriole and of the choroid (Fig. 3), some vascular changes in the inferior temporal quadrant; no significant angiographic abnormalities were found in the right eye.

Therefore, the clinical diagnosis of SS in this patient was substantiated by presence of typical clinical triad, including ischemic retinopathy, sensorineural hearing loss and specific CNS lesions in deep white matter and callosal body. RTX monotherapy (1500 mg total dose) aimed at achieving complete CD19+ B cell depletion (0%) was chosen as therapeutic strategy based on undulating and slowly progressive nature of the illness and favorable tolerability of the drug. As result of the treatment, clinical remission was achieved. The maintenance therapy was repeated treatment with RTX at a dose of 500 mg. Subsequently, clinical sings of SS did not recur.

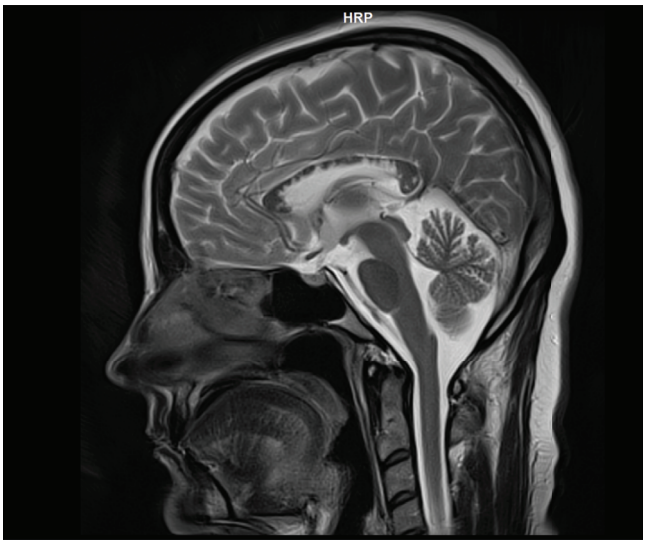


***Fig. 1**. Brain MRI before treatment (sagittal section, T2-WI): multiple hyperintensive 2–4 mm focal lesions in the lower callosal body*

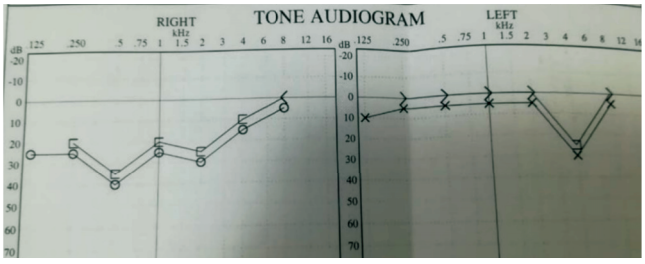
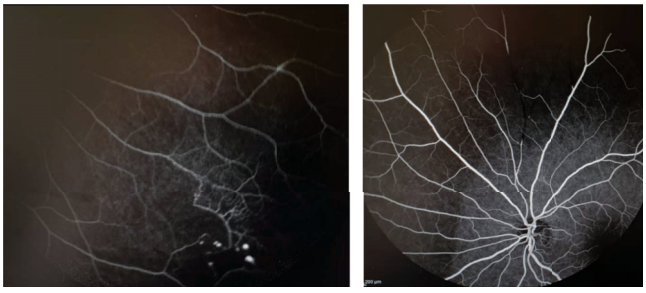


***Fig. 2**. Audiogram: reduced perception of low frequencies in the right ear*



a *b*

***Fig. 3.** Fluorescent angiography: visible infiltrates along the vessels (a) and compromised blood flow in the arteriole (b)*

Discussion

The results of brain MRI, retinal fluorescent angiography and audiometry revealing typical changes in the presented clinical case were of key importance for the confirmation of SS diagnosis. The brain MRI pattern in SS look very similar to MRI findings in MS patients, including multiple focal lesions in periventricular and deep white matter as well as in callosal body. In SS focal lesions are typically located in the central part of callosal body, visualized in T2-WI MRI as "pearl necklace" or "snow-ball", as demonstrated in presented clinical case, and are considered pathognomonic for SS [3, 6, 8, 9]. Callosal body atrophy can eventually be seen in patients at late SS stage. In some SS cases focal lesions are found in basal ganglia,

and intensive contrast matter accumulation in brain membranes is documented in 30% of T1-WI MRIs [3, 8]. Moreover, SS involvement of cervical spinal cord has also been described [10]. Cerebrospinal fluid abnormalities commonly include slight lymphocytic pleocytosis and moderate increase of protein concentration [2].

Fluorescent angiography displays multiple branch retinal artery occlusions and arteriolar wall hyperfluorescence, which is also a pathognomonic sign of SS [11]. Since retinal macular region remains intact in SS, patients can still have normal visual acuity. Optical coherence tomography of the retina is useful for dynamic monitoring of SS-associated retinopathy and for differential diagnosis with multiple sclerosis, as diffuse thinning of the nerve fiber layer is typical for the latter, while SS retinopathy is spotty [12].

Damage to the auditory nerve leads to hearing loss, subtle in most cases, but identifiable by audiometry as typical decrease in perception of low frequencies, as in the presented case.

SS as extremely rare disease has not been studied in randomized clinical trials. SS therapy includes ultra-high doses of GCs (1 g a day intravenously (IV), and 1 mg/kg a day orally), in combination with cyclophosphane (CP) or mycophenolate mofetil (MMF) and RTX [7, 13, 14]. In contrast to multiple sclerosis, positively responding to β-interferons and natalizumab, these agents can cause worsening of clinical symptoms in SS patients [15, 16], which emphasizes the importance of differential diagnosis between the two conditions. Treatment duration varies from several months to several years depending on SS severity.

Pilot recommendations for SS therapy based on accumulated clinical experience with a relatively large cohort of patients were published in 2018 by a group of American researchers [7]. They proposed to modify treatment regimen based on the severity of CNS damage, although RTX is envisaged in all regimens. Repeated courses of RTX in combination with ultra-high doses of IVIGs and IVGCs, CP or MMF (and sometimes with tacrolimus) are recommended in severe cases. In mild CNS involvement treatment choices are less aggressive and limited to GCs, MMF and reduced course of IVIGs while RTX therapy is optional, not necessary. A balanced assessment of associated potential benefit/risk ratio is strongly recommended prior to initiation of aggressive immunosuppressive regimens. Because SS course is often complicated by severe damage to the retina, inner ear and central nervous system (with potential development of mental disorders), patients with SS must be treated promptly and aggressively [7, 14]. The case presented in this paper demonstrated a relatively benign, fluctuating, slow course of the disease, and therefore RTX monotherapy was chosen as a therapeutic strategy.

SS has significant similarities with livedoid vasculopathy (LV) [17], since microvasculature occlusive endotheliopathy becomes the key pathological substrate in both conditions. In the context of LV, it is interesting that skin lesions in SS have been described, including livedo reticularis and a micropapular eruption which responded promptly to treatment with IVIGs, GCs, and RTX [18, 19]. Of importance is the published evidence of successful RTX-based anti-B cell therapy in several LV cases [7, 18–20], including own authors' experience [21]. Anti-B cell therapy that causes B cell depletion in blood and target organs is effective in a wide range of immuno-inflammatory rheumatic diseases [22]. Its efficiency is determined by various mechanisms, suppression of pathogenic autoantibody synthesis, and modulation of the function of B cells (antigen presentation, cytokine synthesis, and costimulation), T lymphocytes and dendritic cells. There is reason to suggest a protective effect of B cell depletion in relation to microvasculature occlusive endotheliopathy. However, the nature and mechanisms of these pleiotropic effects remain unclear.

These publications provide additional support for choosing RTX monotherapy in SS patients, especially in non-severe cases or at early SS stages. Limited use of aggressive immunosuppressants and GCs regimens is important to reduce the risk of adverse reactions, sometimes competing in their severity with SS symptoms.

Conclusion

It can be speculated that the indications for RTX and other biologics that target B cells treatment will expand in the near future. Current data on RTX highlights its relevance to SS. The focus of RTX monotherapy should be targeted at SS cases with contraindications for GCs and cytostatics use, slow-progressive SS or at early stages.

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