

Short Communication

Susac syndrome and multifocal motor neuropathy first manifesting in pregnancy

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Susac Syndrome (SS) and multifocal motor neuropathy (MMN) are rare autoimmune neurological conditions which can affect women of childbearing years. The effect of pregnancy on these disorders is poorly characterised. We report a case of SS first manifesting in pregnancy with challenges in diagnosis and management and a poor clinical outcome, and a case of MMN manifesting in pregnancy then relapsing in a subsequent pregnancy. A summary of other cases in the literature and the postulated underlying immune mechanisms is presented.

Key words: autoimmunity in pregnancy, multifocal motor neuropathy, susac syndrome.

Autoimmune conditions commonly affect women of childbearing years, and it can be difficult to predict the pattern of such diseases during pregnancy. Relapse rates of lupus tend to increase during pregnancy,¹ whereas in contrast, relapses of multiple sclerosis and rheumatoid arthritis reduce during pregnancy, however, often increase postpartum.^{2–4} Myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP) have previously been reported to deteriorate during pregnancy.^{5,6} The effects of pregnancy on other rare autoimmune disorders are less well understood. We report two cases of rare autoimmune neurological conditions, Susac Syndrome (SS) and multifocal motor neuropathy (MMN), which first manifested in pregnancy, and in the case of MMN, relapsed in a subsequent pregnancy.

Case 1

A 28-year-old female primigravida presented at nine weeks' gestation of a twin pregnancy with a one-week history of lower limb weakness, drowsiness and dysarthria. Her past medical history included stable epilepsy from a perinatal left middle cerebral artery ischaemic event. Examination revealed generalised hyperreflexia with ankle clonus and extensor plantar responses bilaterally. She had moderate global weakness, with MRC power of grade 3/5 in all four limb muscle groups with ataxia. Full blood count,

coagulation profile, vasculitic screen, antineuronal antibodies, lupus anticoagulant screen and anticardiolipin antibodies were either normal or negative. MRI brain showed T2 and fluid attenuated inversion recovery (FLAIR) abnormalities with an unusual pattern of meningeal enhancement after Gadolinium (Fig. 1). Serial MRI showed progressive lesions in the deep white matter, including the basal ganglia and cerebellar peduncles with enhancing lesion in the corpus callosum that progressed to volume loss. CSF analysis showed a raised protein of 2000 mg/L ($n < 500$) and normal CSF to serum IgG index without oligoclonal bands, and a raised white cell count (WCC) of $9 \times 10^6/L$ ($n < 5$) which were 100% mononuclear cells. The CSF protein and WCC remained elevated on subsequent analyses performed at eight weeks and four months. She was treated with methylprednisolone (1 gram daily intravenously for three days); however, she deteriorated with fluctuating consciousness and hallucinations. There was evidence of an encephalopathy on electroencephalogram. A core brain biopsy showed foci of myelin loss with varying degrees of axonal loss consistent with microscopic white matter ischaemic foci. There was also focal rarefaction with non-specific gliosis, demyelination and foamy histiocytes. A single vessel was seen in the core biopsy, which showed lymphocytic infiltration. Staining for JC virus and fluorescence *in situ* hybridisation assay for Epstein Bar virus was negative. She remained confused and intermittently agitated despite five more days of intravenous methylprednisolone followed by plasma exchange (six exchanges performed on alternate days) and intravenous immunoglobulin (IVIg, 2 g/kg over five consecutive days).

At 13 weeks' gestation, a pelvic ultrasound confirmed one viable fetus. In the context of her poor response to therapy, a case conference involving the hospital ethics

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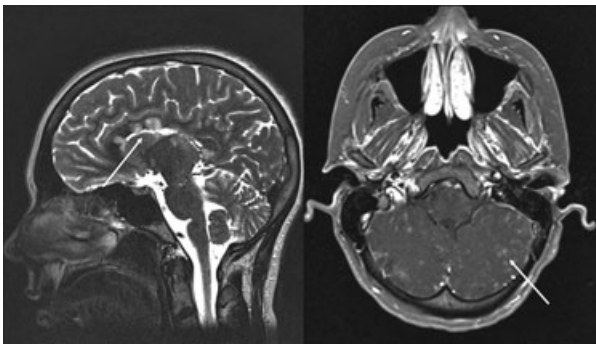


Figure 1 For case 1: T2-weighted MRI of the brain. Sagittal view with an arrow showing lesions in the corpus callosum (left). Axial view following IV gadolinium with arrows showing linear defects demonstrating leptomeningeal enhancement in the cerebellar folia (right).

committee, the Adult Guardian and the patient's family was held. A surgical therapeutic abortion was carried out at 15 weeks' gestation based on the consensus opinion that continuation of pregnancy posed a significant risk to the patient's health. Post-termination of pregnancy, there was ongoing fluctuation characterised by periods of confusion despite ongoing treatment with methylprednisolone therapy.

Twelve weeks after her initial presentation, she developed tinnitus, deafness, headaches and visual hallucinations. Audiogram showed moderate bilateral sensorineural hearing loss. Ophthalmological examination revealed sclerosed blood vessels and branch retinal artery occlusions. At this stage, a clinical diagnosis of SS was made based on the development of ocular and auditory features in addition to the elevated CSF protein and MRI changes. She was treated with oral prednisone (1 mg/kg/day for one month then slowly reduced over the following six months), mycophenolate mofetil 1 gram twice daily and monthly IVIG (IVIG 0.4 g/kg). Aspirin and nimodipine were commenced in view of the branch retinal artery occlusion.

Alternative diagnoses such as amniotic fluid emboli were considered; however, the characteristic clinical picture culminating in encephalopathy, deafness and branch retinal artery occlusions with supportive imaging and CSF findings was consistent with the diagnosis of Susac syndrome. Furthermore, both clinically and on serial neuroimaging, there was evidence of ongoing disease supporting an ongoing inflammatory process. The neuropathology showed areas of infarctions, and perivascular lymphocytes supporting Susac syndrome but did not show characteristic endothelial changes that may have been due to the limitations of the sample such that only one vessel was seen in the core biopsy.

Currently, three and a half years after the onset of illness, cognitive deficits have persisted and her hearing and vision remain impaired. Her upper and lower limbs are moderately weak with ataxia and spasticity. Her

mobility is limited, and she relies on assistance with most activities of daily living.

Case 2

A 32-year-old female presented at 26 weeks' gestation with a 6-week history of slowly progressive asymmetric distal weakness. Examination revealed bilateral, asymmetric, severe weakness of foot dorsiflexion (MRC grade 0/5 on the right and 2/5 on the left) consistent with bilateral peroneal neuropathies. Finger abduction was mildly weak (4/5 bilaterally) consistent with bilateral ulnar neuropathies. There was generalised hyporeflexia. There were no sensory or autonomic symptoms or signs. Haematological, biochemical and standard thyroid and autoimmune investigations were unremarkable. Antinuclear antibodies and erythrocyte sedimentation rate were normal. Serum acetylcholine receptor antibodies were negative. Anti-Ganglioside GM1 IgG assay was six units (<10) and IgM was 15 units (<15). CSF glucose, protein and cell count was unremarkable. There was no evidence of local immunoglobulin synthesis in the CNS.

Nerve conduction studies showed reduced amplitude of the ulnar and peroneal motor responses bilaterally with prolonged ulnar F wave latencies consistent with proximal conduction block. Sensory studies were normal, and needle electromyography showed active denervation in multiple distal upper and lower limb muscles (see supplementary table for more details).

An immune-mediated motor neuropathy was suspected, and treatment with IVIG was commenced with 0.4 g/kg/day for five consecutive days, followed by maintenance therapy with 0.4 g/kg at four weekly intervals throughout the pregnancy. The foot drop improved in power (4/5 on the right, 5/5 on the left), and finger adduction improved to 5/5 bilaterally.

At full term, a healthy liveborn male neonate with no neurological deficit was delivered by elective caesarean section. Postpartum, the woman had residual mild foot drop on the right, muscle cramps and fatigue. She continued on monthly IVIG, and she was able to return to work in a call centre.

During a second pregnancy at age 34 years, the woman developed new weakness at 20 weeks' gestation. There was weakness of finger abduction (right 3/5 and left 2/5), left thumb abduction (3/5) and extension of the left wrist (3/5), and fingers (2/5) and also right finger extension (4/5), consistent with bilateral ulnar nerve, bilateral radial nerve and left median nerve involvement. Foot dorsiflexion remained unchanged. Nerve conduction studies showed reduced amplitudes in the left median motor, bilateral ulnar and left radial nerve motor responses. Distal segment conduction block was evident in the left median and right ulnar nerves. There was a prolonged right ulnar F wave response of 65 milliseconds (<30 ms) suggesting proximal conduction block. The frequency of IVIG was increased from monthly to weekly for the remainder of the pregnancy, and there was no further deterioration. Elective caesarean

section was performed at 34 weeks' gestation, and a healthy live female neonate with no neurological deficit was delivered with no complications.

Postpartum, the patient was maintained on monthly IVIG and methotrexate. The upper limb weakness showed minimal improvement, and she has residual left finger and wrist drop (finger and wrist extension 3/5), weakness of right finger abduction (3/5) and left thumb abduction (3/5). At age 38, she developed autoimmune thyrotoxicosis with positive TSH receptor antibodies, which was treated with carbimazole. She is currently euthyroid and remains clinically stable with moderately severe distal upper limb weakness bilaterally on gradually reducing doses of methotrexate and monthly IVIG.

The diagnosis of MMN was based on the clinical finding of subacute onset of asymmetric and patchy motor weakness without sensory changes, supported by the electrophysiology findings of multiple areas of motor neuropathy with proximal and distal conduction block. This is consistent with the criteria proposed by European Federation of Neurological Societies/Peripheral Nerve Society.⁷

Chronic inflammatory demyelinating polyneuropathy and MMN were considered in the differential diagnosis for this woman's motor weakness without sensory or autonomic involvement. Due to the evidence of conduction block in the absence of objective sensory disturbance, a clinical diagnosis of MMN was made. Atypical pure motor CIDP was also considered but thought to be less likely than MMN due to the normal CSF protein. Also, the former tends to cause proximal weakness rather than the distal weakness commonly seen in MMN.⁸ The absence of GM1 antibodies did not preclude the diagnosis of MMN as they are found in only 30–80% of patients.^{9,10} Other causes such as lead neuropathy and inherited disorders were excluded due to the lack of exposure and the subacute presentation.

Discussion

These two cases highlight the onset of a severe autoimmune neurological disease during pregnancy. Susac Syndrome is a rare disorder characterised by the clinical triad of vision loss, hearing loss and encephalopathy thought to be due to autoimmune-mediated vascular endothelial injury affecting the retinocochleocerebral vasculature.^{11,12} There are no established diagnostic criteria, but the above clinical triad with additional features, including the characteristic ophthalmoscopic finding of branch retinal artery occlusion, and T2 MRI brain changes involving the white matter, grey matter and leptomeninges (Table 1), are supportive of the diagnosis.

Susac Syndrome is often an aggressive disease with potential long-term disability arising from blindness, deafness and neurological impairment. There is limited data on how pregnancy affects the course of SS. In a small case series, three pregnancies were associated with no deterioration, and one was followed by a relapsed in the postpartum period.¹³ A further case report, similar to ours, describes a 25-year-old woman with disease onset at

Table 1 Key features of Susac syndrome. Information adapted from Susac's syndrome: 1975–2005 microangiopathy/autoimmune endotheliopathy, Susac 2007.¹²

Key features of Susac syndrome	
Sex ratio	Female preponderance (3:1)
Clinical triad	Encephalopathy, branch retinal artery occlusions (BRAO) and hearing loss
Other clinical features	Multifocal neurological findings, headache, psychiatric disturbances, cognitive changes, memory loss and confusion
MRI brain features	Distinctive white matter lesions, always involving the corpus callosum. Linear defects and round lesions involving cortical, deep grey matter and leptomeninges
Ophthalmoscopic features	BRAO may show the pathognomonic multifocal fluorescence on fluorescein angiography. Gass plaques are frequently present and reflect endothelial damage
Brain biopsy	Microinfarction with endothelial changes. Non-specific periarteriolar chronic inflammatory cell infiltration
Management options	Immunosuppressant therapy with steroids, cyclophosphamide and intravenous immunoglobulin, usually in combination. Aspirin for BRAO.

Table 2 Clinical criteria for multifocal motor neuropathy (MMN). Adapted from European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of MMN. Joint Task Force of the EFNS and the PNS.⁷

Clinical criteria for multifocal motor neuropathy	
Core criteria (both must be present)	
1	Slowly progressive or stepwise progressive, focal, asymmetric limb weakness, that is, motor involvement in the motor nerve distribution of at least two nerves, for more than 1 month
2	No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs
Supportive clinical criteria	
3	Predominant upper limb involvement
4	Decreased or absent tendon reflexes in the affected limb
5	Absence of cranial nerve involvement
6	Cramps and fasciculations in the affected limb
7	Response in terms of disability or muscle strength to immunomodulatory treatment
Exclusion criteria	
8	Upper motor neurone signs
9	Marked bulbar involvement
10	Sensory impairment more marked than minor vibration loss in the lower limbs
11	Diffuse symmetric weakness during the initial weeks

20 weeks' gestation.¹⁴ Our case of SS illustrates the challenging ethical issues surrounding therapeutic abortion if continuation of pregnancy poses a major risk to the mother's health. A further challenge is the choice of immunosuppressive agent in pregnancy due to the risk of fetal harm posed by commonly used agents. There are no controlled studies of treatment in SS; however, aggressive treatment is generally required. Corticosteroids, cyclosporine, cyclophosphamide, IVIG, methotrexate, MMF and azathioprine have been used in various combinations.¹⁵ A case series of SS patients¹³ described therapeutic abortion in 2 of 4 pregnancies, one directly due to disease activity and the other to allow the safe use of cyclophosphamide.

Multifocal motor neuropathy is an acquired progressive, predominantly distal, motor neuropathy.¹⁶ The electrophysiological hallmark is conduction block in motor nerves. Electrophysiological criteria have been defined⁷ and are considered diagnostic when seen in conjunction with the clinical features outlined in Table 2. MMN is associated with HLA-DRB1*15 and IgM antibodies to the glycolipid GM1 can be detected in approximately 50% of patients,¹⁷ suggesting that B cells and complement play a role in pathogenesis. A Cochrane systematic review on the treatment of MMN concluded that IVIG produces significant short-term improvement in strength.¹⁸ Although there are previous reports of worsening of MMN in pregnancy,¹⁹ this is the first case report to our knowledge of MMN first manifesting in pregnancy. A series of 3 cases of MMN in pregnancy suggested IVIG improves strength during pregnancy.¹⁹

These cases illustrating rare autoimmune neurological conditions first manifesting in pregnancy raise questions regarding the immunological mechanism. It has been postulated that during pregnancy, hormonal changes, including estradiol, progesterone, hCG, cortisol, and other factors, including vitamin D and IL10, are drivers of immunomodulation to prevent fetus rejection.²⁰ The initial predominant immune cellular response (Th1 type) is decreased, whereas humoral response (Th2 type) is increased.²⁰ These changes may drive increased autoantibody production, and thereby exacerbate or unmask various autoimmune conditions as has been previously reported in MG and CIDP.^{5,6} We now add SS and MMN as neurological diseases that could worsen during pregnancy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Investigations.