CASE REPORT

Isaacs' syndrome in pregnancy

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SUMMARY

Isaacs' syndrome is a rare neuromuscular disorder of continuous muscle fibre activity resulting from peripheral nerve hyperexcitability. Symptoms commonly include myokymia (muscle twitching at rest), pseudomyotonia (delayed muscle relaxation), muscle cramps and stiffness. It is caused by voltage-gated potassium channel dysfunction and may be inherited or acquired. Treatment commonly includes anticonvulsants, immunosuppressive therapy and plasma exchange. To date only two cases of Isaacs' syndrome in pregnancy have been reported. We present a case of maternal Isaacs' along with a review of the literature. There are few reports of Isaacs' syndrome in pregnancy, but all are associated with favourable outcomes. Given the autosomal dominant inheritance pattern, genetic counselling of the gravida is recommended. Anticonvulsant may have to be used in pregnancy, and given the potential teratogenicity with several of these agents; preference should be given to newer drugs such as lamotrigine.

BACKGROUND

Isaacs' syndrome is a rare disorder characterised by impaired muscle relaxation after contraction, cramps, stiffness and fasciculations.¹ Symptoms are caused by peripheral nerve hyperexcitability resulting from voltage-gated potassium channelopathy.² This condition may be inherited or acquired.¹ The inherited form is associated with episodic ataxia type 1, an autosomal dominant disorder that involves a point mutation in the KCNA1 gene, which encodes a voltage-gated potassium channel (VGKC) subunit.^{2 3} More commonly Isaacs' syndrome is acquired and many patients have antibodies directed against VGKC associated proteins.⁴ The acquired form is usually seen in association with autoimmune disorders, infections, medications, toxin exposure¹ and cancer.^{2 5} One report describes onset of Isaacs' during pregnancy.⁶

Diagnosis of Isaacs' syndrome is made principally by needle electromyography (EMG) studies which show myokymic and neuromyotonic discharges. Myokymic discharges fire repeatedly at 50–150 Hz and appear as doublet, triplet or multiplet single unit discharges with a high-intraburst frequency.^{1 2 7} Neuromyotonic discharges fire at 150–300 Hz, begin and end abruptly, and their amplitude often fades.^{1 7} Fasciculations and fibrillation potentials are also often present.¹

To date, there are only two reports of Isaacs' syndrome in pregnancy.^{6 8} Therefore our aim was to present our case and provide a review of the literature on maternal Isaacs' syndrome in pregnancy.

CASE PRESENTATION

An 18-year-old Hispanic/Latina female patient, gravida 1 para 0, was referred at 13 weeks to our Maternal-Fetal Medicine clinic for a pregnancy complicated by Isaacs' syndrome. Her medical history was significant only for the Isaacs' syndrome (acquired type), and otherwise negative including for autoimmune disorders. Her family history was only positive for type 2 diabetes mellitus and chronic hypertension, but otherwise negative for any other illnesses including Isaacs' syndrome or autoimmune disorders.

The patient's diagnosis was made 9 years earlier after extensive work up for intermittent twitching in all four extremities, albeit more intense in the legs. Serological evaluation was positive only for VGKC autoantibodies. Motor nerve studies demonstrated slowed conduction velocities, while intramuscular monopolar needle recordings yielded large and long-lasting polyphasic motor unit potentials with reduced recruitment. She had remained under the care of a neurologist, and her disease was well controlled with carbamazepine 400 mg daily, which was continued throughout the pregnancy without any dose adjustments. She remained asymptomatic through the antepartum and intrapartum periods.

OUTCOME AND FOLLOW-UP

She ultimately underwent a 39-week spontaneous vaginal delivery of a healthy 3310 g female infant with normal APGAR scores. She did receive regional anaesthesia (epidural) without complication. As of 6 weeks postpartum, she had an uneventful course and was doing well with ongoing carbamazepine therapy.

DISCUSSION

Isaacs' syndrome is a rare neuromuscular disorder characterised by peripheral nerve hyperexcitability resulting from a voltage-gated potassium channelopathy. Patients commonly experience myokymia, impaired muscle relaxation, cramps and stiffness.¹ Sweating, paraesthesias, muscle hypertrophy and progressive muscle weakness are other less commonly reported symptoms.⁹ Some severe cases may involve central nervous system (CNS) impairment resulting in anxiety, memory loss, sleep disturbance and hallucinations.^{5 10} Patients with the triad of neuromyotonia, encephalopathy and hyperhidrosis are considered to have Morvan syndrome.² Some reports identify Isaacs' syndrome synonymously with neuromyotonia,¹ while others report Isaacs' syndrome more specifically as an acquired neuromyotonia.^{4 7 11} Other terms referring to this disorder include continuous muscle fibre activity

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syndrome,¹² Quantal Squander syndrome, Armadillo syndrome, Mertens' syndrome, Mertens-Isaacs' syndrome, neurotonia, myotonia with impaired muscular relaxation and generalised myokymia.¹

Isaacs' syndrome is caused by dysfunctional VGKCs in peripheral nerves² and may be inherited or acquired.¹⁻⁹ The inherited form is much less common, and has been associated with point mutations in the KCNA1 gene on chromosome 12,²⁻⁹ which encodes the K⁺ channel subunit hKv1.1.³ Mutations of this KCNA1 gene are commonly found in episodic ataxia type 1 which demonstrates an autosomal dominant mode of inheritance.³

Isaacs' syndrome is most commonly acquired and associated with autoimmune disorders such as myasthenia gravis,¹ Lambert-Eaton myasthenia syndrome,¹³ Hashimoto thyroiditis, Addison disease, vitiligo, vitamin B₁₂ deficiency, coeliac disease, rheumatoid arthritis^{2-4 10} and Guillain-Barre syndrome.¹⁻⁹ It has also been associated with infection,¹ drugs such as penicillamine,² exposure to toxins¹ and pregnancy.⁶ In some patients, Isaacs' may demonstrate a paraneoplastic aetiology especially with thymoma or small-cell lung carcinoma.²⁻⁵

About 40% of patients with Isaacs' syndrome have detectable antibodies to VGKCs.¹ These antibodies are directed against proteins that form a complex with VGKCs such as LGI1 and Caspr2 as well as other unknown proteins.⁴ LGI1 is localised to CNS synapses and Caspr2 organises VGKC's on both central and peripheral nervous system axons.^{4 11} The antibodies do not directly affect VGKC kinetics but rather act to decrease channel density on nerve terminals.⁷ VGKCs are important in nerve terminal repolarisation after action potential.³

Only two cases of Isaacs' syndrome during pregnancy have been reported, both of which had a favourable outcome. In 1997, Morgan *et al* presented the case of a 30-year-old parturient woman who was diagnosed with Isaacs' syndrome at the age of 19. Her symptoms had been successfully managed with carbamazepine for 11 years. The patient chose to receive epidural analgesia for pain management during labour and did so successfully. She delivered a healthy child at 37 weeks gestation.⁸ Basiri *et al* reported on a patient with chronic inflammatory demyelinating polyneuropathy who developed symptoms of muscle cramps and stiff gait during the fourth month of her pregnancy. She delivered a healthy boy without complications. After unsuccessful treatment with phenytoin and carbamazepine, plasma exchange therapy was initiated and successfully abolished symptoms after 8 weeks. Her child is healthy and does not show evidence of neuromyotonia.⁶

Few reports have addressed anaesthetic management of patients with Isaacs' syndrome. In at least one patient with neuromyotonia, lumbar epidural anaesthesia with 11.5 mL of 2% carbocaine effectively reduced myokymic discharges.¹⁴ Peripheral nerve hyperexcitability persists in sleep, spinal anaesthesia and general anaesthesia.¹⁵ Peripheral nerve block has varying effects ranging from abolishment of abnormal activity to no effect.¹⁶

Treatment of this disorder commonly includes anticonvulsants such as phenytoin, carbamazepine, gabapentin, sodium valproate, lamotrigine and acetazolamide.^{1-4 8 17} Botulinum toxin type A has also been successful in symptom management.^{17 18} Plasma exchange, immunoglobulin therapy and immunosuppression may also be effective treatments in patients with the autoimmune form of Isaacs'.^{5 10}

While anticonvulsant drugs may be useful in managing symptoms of Isaacs' syndrome, they may present risks to the mother and fetus. The risk of birth defects is increased by anticonvulsants valproic acid, carbamazepine, phenytoin and lamotrigine,

but the type and severity of defect differs among these medications. Valproic acid has been associated with increased risk of neural tube and cardiac defects, cleft palate and hypospadias.^{19 20} Carbamazepine may present increased risk of neural tube defects, but is not associated with cleft palate or hypospadias.¹⁹ Newer antiepileptic drugs such as lamotrigine and gabapentin likely present fewer risks to the fetus.²⁰ At least one case of anticonvulsant hypersensitivity has been reported during pregnancy, with the pregnant patient developing symptoms of maculopapular rash, fever and eosinophilia approximately 4 weeks after starting carbamazepine therapy. Carbamazepine was discontinued and the patient was given phenobarbital. Her symptoms persisted with phenobarbital and she switched to gabapentin. Thereafter her symptoms resolved.²¹ Anticonvulsant hypersensitivity is most commonly caused by aromatic anticonvulsants such as phenytoin, carbamazepine and phenobarbital, but has also been reported with use of newer anticonvulsants such as lamotrigine. The incidence of this reaction in pregnant patients has not yet been established.²¹

Learning points

- Isaacs' syndrome in pregnancy is associated with favourable outcomes.
- The parents need genetic counselling given that some cases are inherited.
- With respect to treatment, should anticonvulsant therapy be required, consideration should be given to newer agents with a more favourable teratogenicity profile.
- Timing and mode of delivery should be reserved for usual obstetrical indications.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Maddison P. Neuromyotonia. *Clin Neurophysiol* 2006;117:2118–27.
- 2 Rana S, Ramanathan R, Small G, *et al*. Paraneoplastic Isaacs' syndrome: a case series and review of the literature. *J Clin Neuromuscul Dis* 2012;13:228–33.
- 3 Falace A, Striano P, Manganelli F, *et al*. Inherited neuromyotonia: a clinical and genetic study of a family. *Neuromuscul Disord* 2007;17:23–7.
- 4 Fleisher J, Richie M, Price R, *et al*. Acquired neuromyotonia heralding recurrent thymoma in myasthenia gravis. *JAMA Neurol* 2013;70:1311–14.
- 5 Vernino S. Chapter 14: peripheral nerve hyperexcitability and the neuromuscular junction. In: Engel A, ed. *Handbook of clinical neurology*. 91st edn. The Netherlands: Elsevier, 2008:433–43.
- 6 Basiri K, Fatehi F, Chitsaz A. Isaac's syndrome associated with CIDP and pregnancy. *Arch Iran Med* 2011;14:206–8.
- 7 Arimura K, Sonoda Y, Watanabe O, *et al*. Isaacs' syndrome as a potassium channelopathy of the nerve. *Muscle Nerve Suppl* 2002;25:S55–8.
- 8 Morgan P. Peripartum management of a patient with Isaacs' syndrome. *Can J Anesth* 1997;44:1174–7.
- 9 Myers K, Baker S. Late-onset seropositive Isaacs' syndrome after Guillain-Barré syndrome. *Neuromuscul Disord* 2009;19:288–90.
- 10 Newsom-Davis J, Mills K. Immunological associations of acquired neuromyotonia (Isaacs' syndrome): report of five cases and literature review. *Brain* 1993;116:453–69.
- 11 van Sonderen A, Wirtz P, Verschuuren J, *et al*. Paraneoplastic syndromes of the neuromuscular junction: therapeutic options in myasthenia gravis, Lambert-Eaton Myasthenic Syndrome, and neuromyotonia. *Curr Treat Options Neurol* 2013;15:224–39.
- 12 Isaacs H. A syndrome of continuous muscle-fibre activity. *J Neurol Neurosurg Psychiatry* 1961;24:319–25.

- 13 Sinha S, Newsom-Davis J, Byrne N, *et al.* Autoimmune aetiology for acquired neuromyotonia (Isaacs' syndrome). *Lancet* 1991;338:75–7.
- 14 Hosokawa S, Shinoda H, Sakai T, *et al.* Electrophysiological study on limb myokymia in three women. *J Neurol Neurosurg Psychiatry* 1987;50:877–81.
- 15 Thompson P. The stiff-man syndrome and related disorders. *Parkinsonism Relat Disord* 2001;8:147–53.
- 16 Singh H, Tewari A, Bansal A, *et al.* Anaesthesia for a patient with Isaac's syndrome and myasthenia gravis. *Br J Anaesth* 2009;103:460–1.
- 17 ÖZ O, Yucel M, Akgun H, *et al.* Isaacs' syndrome—clinical and electrophysiological response to Botulinum toxin type A. *Noropsikiyatri Arsivi Arch Neuropsychiatry* 2012;49:77–9.
- 18 Ginsburg G, Forde R, Martyn J, *et al.* Increased sensitivity to a nondepolarizing muscle relaxant in a patient with acquired neuromyotonia. *Muscle Nerve* 2009;40:139–42.
- 19 Werler M, Ahrens K, Bosco JLF, *et al.* Use of antiepileptic medications in pregnancy in relation to risks of birth defects. *Ann Epidemiol* 2011;21:842–50.
- 20 Veiby G, Daltveit A, Engelsen B, *et al.* Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014;261:579–88.
- 21 Deering SH, Thompson K, Taylor J, *et al.* Anticonvulsant hypersensitivity reaction in pregnancy. *Obstet Gynecol* 2003;102:1215–17.

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