Isaacs syndrome: the frontier of neurology, psychiatry, immunology and cancer

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Evolution of Isaacs syndrome from case studies that described continuous ectopic activity through to an understanding as a multisystem autoimmune condition

Six decades ago, Dr Hyam Isaacs reported a new clinical syndrome in the *Journal of Neurology, Neurosurgery and Psychiatry*.¹ Isaacs used the term ‘syndrome of continuous muscle-fibre activity’ or the more descriptive ‘armadillo disease’ for the condition which now has become known as Isaacs syndrome or acquired autoimmune neuromyotonia. In his landmark series, Isaacs described a phenotype of progressive muscle stiffness, with widespread fasciculation leading to weakness. A key finding was continuous muscle activity on electromyography, occurring at rest and unaffected by local nerve blockade. The original report also detailed a number of unsuccessful treatment approaches, as well as an astonishing improvement

A syndrome of continuous muscle-fibre activity

Authors: Isaacs H

Year published: 1961

Number of times cited: 480

produced by sodium diphenyl hydantoinate (phenytoin) treatment.

Over the past 60 years, while we have learnt much more about the pathophysiology of Isaacs syndrome, there are still many elements that remain unresolved. A critical factor in understanding the Isaacs jigsaw puzzle came with the identification of the autoimmune basis for the disorder by the group led by John Newsom-Davis and Angela Vincent.² The demonstration of pathogenic immunoglobulin G (IgG) autoantibodies in a patient with severe Isaacs syndrome refractory to treatment, and the successful use of plasma exchange to ameliorate symptoms,² highlighted the role of the immune system in the syndrome and provided another avenue of treatment approaches.

Presently, autoantibodies are identified in a significant proportion (45–50%) of Isaacs syndrome patients.^{3–4} These were initially considered to be antibodies against voltage-gated potassium channels (VGKC), but in the past 10 years the molecular identity of these autoantibodies has been further clarified, with targets revealed to be VGKC-complex proteins including contactin associated protein 2 (CASPR2) and leucine-rich glioma inactivated 1 (LGI1).^{5–6} The molecular identification of these antibodies has revealed a spectrum of overlapping disorders from Isaacs syndrome, through to Morvan’s syndrome and limbic encephalitis.^{7–8} However, the lack of specific antibody targets in the remaining patients suggests that there are likely to be additional autoantibody targets yet to be discovered.

In addition to the classical muscle symptoms of Isaacs syndrome, there is a spectrum of autonomic and central nervous system (CNS) involvement that link Isaacs syndrome to other autoimmune disorders. Sensory symptoms including

paraesthesia and pain and autonomic disturbance including excessive sweating, tachycardia or diarrhoea are reported by almost half of patients.³ CNS symptoms are also prominently reported including insomnia, personality and mood changes, anxiety and depression.^{3–4} There is no specific association of autoantibody type with clinical symptoms—while LGI1 antibodies are primarily associated with limbic encephalitis and CNS involvement, 31% of patients display peripheral involvement including hyperexcitability or neuropathic pain in >20%.⁹ Similarly, CASPR2 antibodies are associated with both CNS and peripheral-predominant clinical presentations,⁹ and associated with neuromyotonia in <40% of cases.¹⁰ Further clinical and molecular phenotyping of large-scale cohorts will be necessary to determine specific associations with neuromyotonia across syndromes.

Underlying the immune basis of Isaacs syndrome there is a prominent association with cancer, with 21–25% of Isaacs syndrome patients diagnosed with recent tumours,^{3–4} highlighting the need to screen carefully for malignancy. In particular, CASPR2 antibodies are associated with thymoma in 20% of cases.¹⁰ The association with cancer suggests that Isaacs syndrome can develop through paraneoplastic mechanisms, with tumour-associated antigens triggering an autoimmune response via cross-reacting antibodies with nerve related epitopes.⁷

In terms of understanding the clinical hallmark of Isaacs syndrome, namely continuous muscle activity, the site of origin for this spontaneous activity remains to be determined. The typical patterns of ectopic activity (figure 1) do not seem to be caused by a generalised disturbance of motor axon membrane excitability.^{8–11–12} Most likely, the activity is generated focally, perhaps at the motor nerve terminal which is relatively unprotected by the blood–nerve barrier, making it vulnerable to autoantibody attack. A proximal or central generator of ectopic activity seems less likely, particularly in the context of normal corticomotor-neuronal integrity as established in acquired

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Figure 1 A raster display of the ectopic activity typical of Isaacs' syndrome, with uniplet, doublet and multiplet discharges recorded at rest. Adapted from Kiernan et al, 2001.¹¹

neuromyotonia patients,¹³ although both a proximal and distal origin of discharges have been recorded.¹⁴

Although vast improvements in treatment and care have been made since Isaacs' report 60 years ago, Isaacs syndrome remains under-recognised, with diagnostic delays, unaddressed symptoms and poor treatment efficacy for some patients. While largely effective, modern day treatments including membrane stabilising drugs typically encountered in epilepsy, as well as immunomodulatory therapies such as plasma exchange and intravenous immunoglobulin, are not effective in all patients.³ We need large-scale, multi-centre studies to understand the complex symptom profile and identify novel treatments for refractory patients. Ultimately, further delineation of the complex phenotypes associated with Isaacs syndrome, understanding of specific autoantibody targets and clarification of the association with cancer will be required to facilitate the development of targeted therapies. These advances will provide the key to

streamlining diagnosis, treatment and care for patients with Isaacs syndrome in the next 60 years.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

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To cite Park SB, Thurbon R, Kiernan MC. *J Neurol Neurosurg Psychiatry* 2020;91:1243–1244.

Received 22 July 2020

Accepted 5 August 2020

Published Online First 2 September 2020

J Neurol Neurosurg Psychiatry 2020;91:1243–1244.
doi:10.1136/jnnp-2020-324675

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