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Severe treatment-refractory antibody positive autoimmune autonomic ganglionopathy after mRNA COVID19 vaccination

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ABSTRACT

Background: COVID-19 vaccine-associated peripheral and central neuroimmunological disorders have been well described. We present the case of a 56 year old male who developed α3-ganglionic AChR antibody positive Autoimmune Autonomic Ganglionopathy (AAG) after completion of a two-dose course of mRNA (Comirnaty) vaccination for COVID19.

Results: A previously hypertensive 56 year old male presented with the subacute onset of severe constipation, urinary retention, erectile dysfunction, sudomotor failure, sicca symptoms, non-reactive pupils and severe orthostatic hypotension shortly after receiving the second dose of an mRNA vaccine against COVID19. Autonomic testing revealed severe cardiovagal, adrenergic and sudomotor impairment, and tonic 'half-mast' pupils with evidence of sympathetic and parasympathetic denervation. Pathological α3-ganglionic ACHR antibodies were positive in serum as detected by a new flow cytometric immunomodulation assay. Malignancy was excluded. The patient was diagnosed with severe, treatment-refractory acute AAG.

Conclusions: While autonomic dysfunction has been previously reported post-COVID19 vaccination, to our knowledge this is the first reported case of antibody-positive AAG in this setting. The severity of this case is in marked contrast to the existing literature on idiopathic antibody-positive autoimmune pandysautonomia.

Dear Editor,

We report, to our knowledge, the first documented case of anti-a3-ganglionic acetylcholine receptor antibody positive autoimmune autonomic ganglionopathy (AAG) after vaccination with the novel Comirnaty mRNA SARS-CoV2 vaccine.

A patient in their 50s presented thirty-five days after completion of a primary vaccination course with Comirnaty mRNA vaccine with subacute severe pandysautonomia. The only medical history was of hypertension. He had initially developed light intolerance, anisocoria and a tonic right pupil, then orthostatic symptoms, including syncope, then profound abdominal bloating and constipation. On day thirty-five, he presented to our hospital with recurrent presyncope, constipation and urinary retention. Early satiety, erectile dysfunction, xeroderma of the hands and feet, and sicca symptoms were evident on history taking. On examination, the systolic blood pressure was 110/68 mmHg and fell to unrecordable levels on standing without heart rate variation. Unresponsive midsized pupils, xerostomia and axillary anhidrosis were noted. The neurological examination was otherwise normal, including assessment for possible movement disorders. Nerve conduction studies were within normal limits. Ophthalmologic assessment demonstrated Adie pupils and Horner syndrome bilaterally on dilute pilocarpine and apraclonidine testing, respectively [1]. A Schirmer's test revealed significant ocular dryness.

Cardiac investigations revealed no structural abnormalities or arrhythmias. Hormonal evaluation, including pituitary, thyroid and adrenocortical function was normal, although there was no serum metanephrine response to postural hypotension. Diabetes mellitus, syphilis and HIV were excluded, and antinuclear, ganglioside, limbic encephalitis and onconeural paraneoplastic antibodies were absent. Cerebrospinal fluid (CSF) analysis demonstrated normal protein, glucose and cell counts.Magnetic resonance imaging of the brain and whole spine and computed tomography of the neck, chest, abdomen and pelvis were unrevealing. On autonomic testing, tilt-table testing demonstrated a drop in blood pressure from 140/90 mmHg supine to 54/35 mmHg after two minutes at 60 degrees, with no heart rate response (Fig. 1). There was no heart rate response to Valsalva manoeuvre and sympathetic skin responses in the hands and feet were absent. Sweat testing demonstrated complete anhidrosis.

Antibodies to whole alpha-3 ganglionic acetylcholine receptor [2] as measured via a novel cell-based immunomodulation assay [3], were positive at 39% modulation (Reference Interval $< 18\%$). In the context of pandysautonomia and positive alpha-3 ganglionic acetylcholine receptor antibodies by a cell-based assay, the patient was diagnosed with definite AAG [4].

Plasma exchange and intravenous immunoglobulin (2 g/Kg) with pulsed methylprednisolone (1 g $\times$ 3) were instituted with minimal response. The patient received an induction course of rituximab. A non-mRNA SARS-CoV2 vaccination booster was given without complication and the patient was then transitioned to mycophenolate mofetil. Fludrocortisone, midodrine and pyridostigmine were initiated to good effect, with reduction in syncopal events.

An incomplete remission has been achieved six months since illness-onset; while orthostatic symptoms have been mitigated, other features of autonomic failure remain present and severe.

To our knowledge, this appears to be the first documented case of antibody-positive AAG temporally associated with vaccination with a

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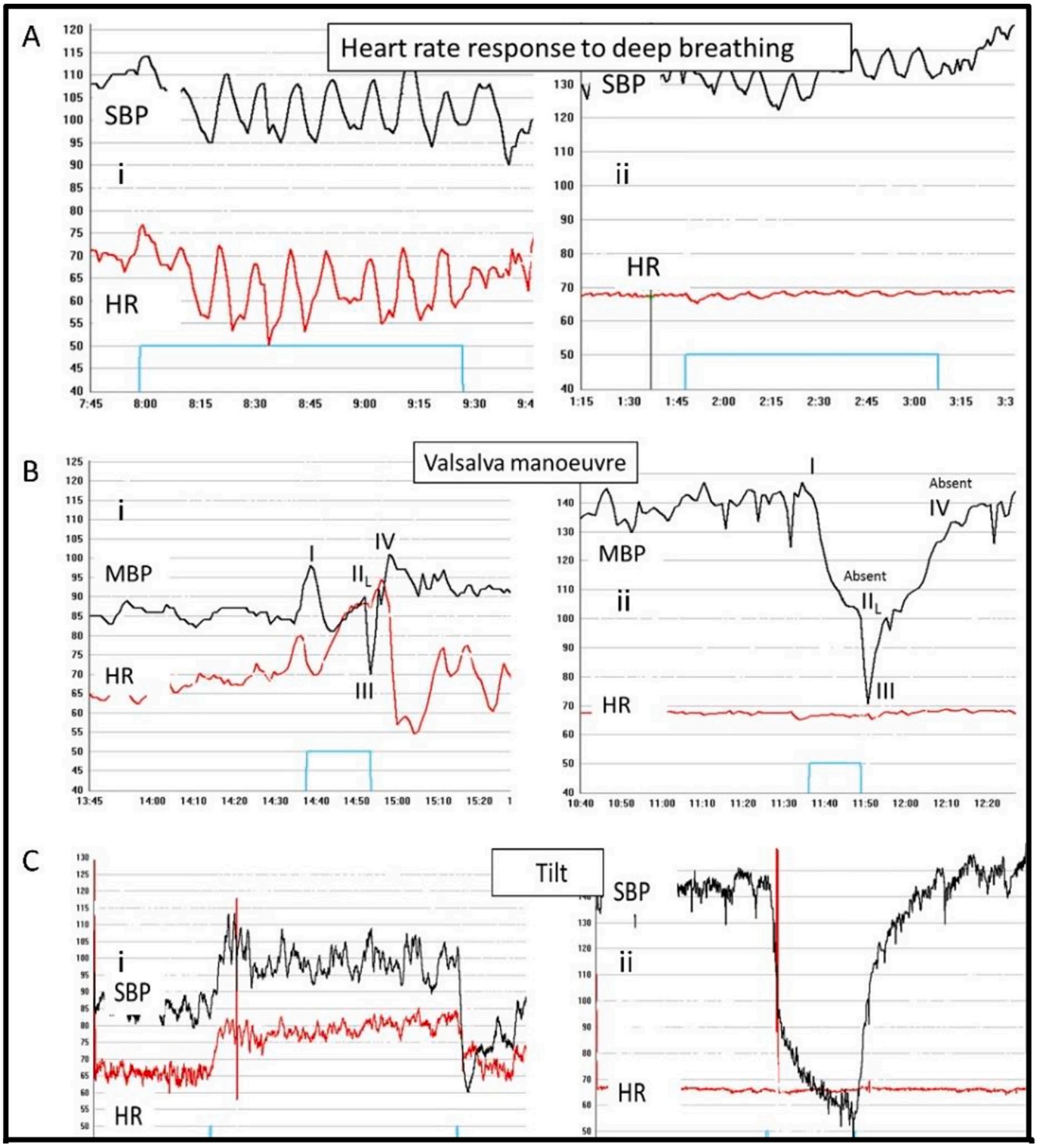

Fig. 1. Autonomic testing – heart rate and blood pressure responses to A) deep breathing, B) Valsalva manouevre and C) tilt table testing in the case subject (ii) vs control (i). (BP in mmHg, HR in bpm, vs time in minutes: seconds).

novel mRNA COVID19 vaccine. Although causation is speculative, this patient had an essentially bland medical history until they developed autonomic failure 5 days after their second vaccination. COVID-19 vaccination induced autonomic dysregulation is plausible, given well-described autonomic dysfunction after COVID-19 illness itself [5]. In contrast to the majority of cases of antibody-positive AAG, which usually demonstrate a prompt and significant response to immunotherapy [6], this case has unfortunately remained relatively refractory to several lines of therapy.

Given the rapid implementation of population-wide use of two novel mRNA vaccines against SARS-CoV2, it is important that clinicians maintain vigilance for rare and potentially severe autoimmune complications of these new therapeutics so that changing incidence patterns – and response to treatment - can be identified.

Author contribution statement

SR collected data and prepared the first draft. NU managed clinical follow-up, collected data, performed and interpreted serologic studies and reviewed the article. JS collected data, performed and interpreted autonomic studies and reviewed the article. All authors gave final approval for the version to be published.

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Declaration of Competing Interest

None declared.

Data availability

No data was used for the research described in the article.

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