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SYNDROME OF INAPPROPRIATE ANTIDIURESIS MAY HERALD OR ACCOMPANY NEUROMYELITIS OPTICA

Aquaporin-4 (AQP4) is the target autoantigen of an immunoglobulin G (IgG) autoantibody that distinguishes a spectrum of inflammatory demyelinating CNS disorders (the neuromyelitis optica [NMO] spectrum) from multiple sclerosis (MS) and other CNS demyelinating disorders.¹ Compelling evidence supports this IgG having a central role in the pathogenesis of NMO. AQP4 is concentrated in astrocytic foot processes at interfaces between CNS parenchyma and fluid compartments, both CSF and blood,¹ and in areas involved in osmosensitivity and osmoregulation, including supraoptic and paraventricular nuclei of the hypothalamus and sensory circumventricular organs, the subfornical organ, the organum vasculosum of the lamina terminalis, and the area postrema.² A single case of the syndrome of inappropriate antidiuresis (SIAD) has been described in NMO.³ Here we report the frequency of SIAD in NMO.

Methods. *Standard protocol approvals, registrations, and patient consents.* The study was approved by the Institutional Review Board. The study involved retrospective chart review of 160 AQP4-IgG seropositive Mayo Clinic patients identified through the Neuroimmunology Laboratory's NMO database who provided consent to have their records reviewed.

Our inclusion criterion, hyponatremic patients fulfilling modified Bartter and Schwartz criteria for SIAD,⁴ required that data be available for both serum sodium concentration and blood/urine osmolality, at the onset of NMO or during a relapse of the disease. We excluded patients whose hyponatremia was attributable to carbamazepine or diuretic therapy (3), lymphoma (1), or thyroid dysfunction (1). No patient had signs of cerebral salt wasting syndrome.

Results. Among 160 patients with NMO or NMO spectrum disorder, 43 had sufficient data for the study. Seven patients (16%) met diagnostic criteria for SIAD (table). The median age at disease onset was 55 years (range 15–72). The median follow-up interval was 67 months (range 24–150). SIAD was

the initial symptom of the attack in 5 of the 43 patients (12%). Hyponatremia was mild (130 mmol/L) in 1 patient, moderate (120–130 mmol/L) in 4, and severe (<120 mmol/L) in 2. Only 1 patient experienced confusion and decreased consciousness attributable to hyponatremia. No information about sodium urinary concentration and plasma vasopressin levels was available. No patient was on any diuretic therapy or had adrenal insufficiency. Creatinine and BUN were unremarkable in all patients. Two patients experienced intractable vomiting, 2 had nausea, and 1 patient developed a syndrome of posterior reversible encephalopathy at the time of documented hyponatremia. Hyponatremia resolved in all patients after fluid intake was restricted to 1 L per day. No patient experienced a recurrence of hyponatremia.

MRI revealed brain abnormalities in 4 patients; 1 had fluid-attenuated inversion recovery and T2-weighted signal abnormalities extending from the brainstem into the area postrema region. Five patients had radiologic signs compatible with longitudinally extensive transverse myelitis, which in 1 developed 3 weeks after SIAD onset. No patient had evidence of hypothalamic abnormalities on brain MRI.

Discussion. This study describes SIAD as an accompaniment of an NMO attack in 16% of cases, and identified SIAD at initial NMO attack in 12%. In 1 case (patient 7) SIAD preceded the NMO relapse by 3 weeks, suggesting that SIAD, in some patients with NMO, may herald a relapse. We are aware that the prevalence of SIAD in our cohort may have been overestimated because we selected only patients with documented information about serum sodium concentration, and blood and urine osmolality. However, the relatively high frequency of SIAD in this NMO cohort contrasts with MS, in which SIAD is rare.

Our database previously revealed that 12% of NMO/AQP4-IgG seropositive patients with NMO seen at Mayo Clinic had intractable vomiting as the initial presenting symptom of NMO.⁵ None of those patients experienced hyponatremia. Nausea and vomiting can be both a symptom and a cause of hy-

Table Clinical characteristics of 7 patients with SIAD in the context of NMO spectrum disorder

Patient	Sex/age at onset, years	Hyponatremia features				Neurologic accompaniment	Timing of SIAD occurrence in disease course	NMO-IgG (IF titer) ^a	Diagnosis at last follow-up	Length of follow-up from onset, months
		Serum sodium concentration, mmol/L	Blood osmolality, mOsm	Urine osmolality, mOsm						
1	F/72	118	270	314	LETM, area postrema lesion	Initial attack	7,680	NMO	24	
2	M/60	130	270	965	LETM with brainstem lesions	Initial attack	Seronegative (CSF positive)	rLETM	46	
3	F/40	127	271	285	LETM, PRES	4th relapse	240	rLETM	74	
4	F/71	126	269	734	LETM, brain lesions	Initial attack	7,680	rLETM	62	
5	F/15	111	265	538	LETM	Initial attack	3,840	NMO	70	
6	F/62	129	269	482	LETM	Initial attack	3,840	NMO	150	
7	F/65	128	273	211	^b	4th relapse	7,680	NMO	46	

Abbreviations: IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; NMO = neuromyelitis optica; PRES = posterior reversible encephalopathy syndrome; rLETM = relapsing longitudinally extensive transverse myelitis; SIAD = syndrome of inappropriate antidiuresis.

^a NMO-IgG detected by indirect immunofluorescence (IF) (negative value is <60).

^b LETM developed 3 weeks after SIAD diagnosis.

ponatremia. Hyponatremia caused by vomiting is hypovolemic which is reflected by an increased blood osmolality. Hyponatremia in the setting of SIAD is euvolemic and hypoosmolar. In 4 of the 7 patients in the present study, vomiting or nausea coincided with SIAD, suggesting a potential role of the area postrema in SIAD. Neurons in the area postrema are osmosensitive and regulate vasopressin secretion.⁶ The 3 patients with SIAD without nausea and vomiting (patients 3, 6, and 7) may have had lesions involving the hypothalamic supraoptic and paraventricular nuclei or other AQP4-enriched circumventricular organs serving osmosensitive functions.

In the mammalian CNS, AQP4 interacts with the transient receptor potential channel, vanilloid subfamily (TRPV4), an osmotically activated ion channel expressed in circumventricular organs. This interaction is essential for TRPV4 to function as an astroglial osmosensor.⁷ Thus SIAD secondary to impairment of an AQP4-coupled TRPV4 channel may represent another pathogenic outcome of IgG interacting with AQP4 in NMO.

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