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Review Article

Hyponatremia in Guillain-Barre Syndrome: A Review of Its Pathophysiology and Management

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ABSTRACT: Guillain-Barre syndrome (GBS) is the commonest cause of acute polyradiculoneuropathy that requires hospitalization. Many of these patients experience systemic and disease-related complications during its course. Notable among them is hyponatremia. Though recognized for decades, the precise incidence, prevalence, and mechanism of hyponatremia in GBS are not well known. Hyponatremia in GBS patients is associated with more severe in-hospital disease course, prolonged hospitalization, higher mortality, increased costs, and a greater number of other complications in the hospital and worse functional status at 6 months and at 1 year. Though there are several reports of low sodium associated with GBS, many have not included the exact temporal relationship of sodium or its serial values during GBS thereby underestimating the exact incidence, prevalence, and magnitude of the problem. Early detection, close monitoring, and better understanding of the pathophysiology of hyponatremia have therapeutic implications. We review the complexities of the relationship between hyponatremia and GBS with regard to its pathophysiology and treatment.

RÉSUMÉ : Hyponatrémie dans le cas du syndrome de Guillain-Barré : une analyse de sa physiopathologie et de sa prise en charge. Le syndrome de Guillain-Barré (SGB) est la cause la plus fréquente de polyradiculoneuropathie aiguë nécessitant une hospitalisation. Plusieurs des patients atteints présentent des complications systémiques liées à une maladie au cours de l'évolution de ce syndrome. L'hyponatrémie est l'une de ces complications. Bien que reconnue depuis des décennies, l'incidence, la prévalence et le mécanisme précis de l'hyponatrémie dans le cas du SGB ne sont pas bien connus. On le sait, l'hyponatrémie chez les patients atteints de SGB est associée à une évolution plus sévère de ce syndrome à l'hôpital, à une hospitalisation prolongée, à une mortalité plus élevée, à des coûts accrus, à un plus grand nombre d'autres complications survenant à l'hôpital et à un état fonctionnel moins favorable au bout de six mois et d'un an. Bien que le manque de sodium ait été fréquemment associé au SGB, nombre d'études n'ont pas inclus la relation temporelle exacte du sodium ou ses valeurs sérielles dans le cas du SGB, sous-estimant ainsi l'incidence, la prévalence et l'ampleur exacte du problème. Une détection précoce, une surveillance étroite et une meilleure compréhension de la physiopathologie de l'hyponatrémie ont pourtant des implications thérapeutiques. Dans cet article, nous entendons donc passer en revue les complexités de la relation entre l'hyponatrémie et le SGB en ce qui concerne sa pathophysiologie et son traitement.

Keywords: GBS; Cerebral salt wasting; Hyponatremia; SIADH; Pathophysiology; Dysautonomia; Prognosis; Management

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Introduction

Guillain-Barre syndrome (GBS) is the most common cause of acute polyradiculoneuropathy and has a high risk of morbidity and mortality[1] and often requires hospitalization. Hyponatremia defined as serum sodium level < 135meq/L is a common abnormality among hospitalized patients. Whether present at admission or acquired during hospitalization hyponatremia is associated with higher mortality and longer hospital stays.[2] The various etiologies of hyponatremia in neurological pratients include the syndrome of inappropriate antidiuretic hormone secretion [SIADH] and cerebral salt wasting syndrome [CSWS].[3] Hyponatremia is especially significant in GBS since autonomic dysfunction is reported in up to two-thirds of patients with GBS[4] and SIADH is a well-known manifestation of dysautonomia.[5] Furthermore, the incidence of hyponatremia in GBS has doubled in the past decade[6] [6.9% in 2002 vs 13.5% in 2011].

The association of hyponatremia in poyradiculitis was first mentioned in 1951[7] and later in 1958 specifically in GBS[8] by Fourman & Leeson. Subsequently, there were a series of case reports and short case series in the 1960s.[8,9] Hyponatremia in GBS patients is associated with more severe in-hospital disease course,[10] prolonged hospitalization, higher mortality, increased costs, and a greater number of other complications in the hospital[6,11] and worse functional status at 6 months and at 1 year.[10]

However, several studies have not included the estimation of sodium or its serial values during the course of GBS, thus underestimating the exact incidence, prevalence, and magnitude of

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the problem. Furthermore, the exact mechanism of hyponatremia remains to be fully understood.

Our aim is to review the literature with regard to the various pathophysiologic mechanisms of hyponatremia and its significance in GBS. This is very crucial when it comes to managing these patients in the face of dysautonomia and its accompanying delicate balance of fluid and electrolytes.

Demography

One of the largest cohorts that examined the incidence of hyponatremia in hospitalized patients with GBS has been 54,778 patients over a 10-year period between 2002 & 2011 from the United States. The incidence was found to be 11.8%.[6] The incidence has been higher in previous studies from India[12], China,[11] Finland,[10] United Kingdom,[13] and New Zealand.[14] Hyponatremia is frequent in severely affected patients with GBS [36.2%] as against mild to moderately affected patients[6] [11.8% & 13%, respectively].

There has been no gender preponderance for hyponatremia in patients with GBS.[15] The mean age of GBS patients with hyponatremia is higher.[6,13,14] Apart from advancing age and severity of disease the other risk factors associated with increased incidence of hyponatremia include diuretic usage, preceding diarrhea, concurrent malignancy,[16] presence of neck flexor weakness,[5] facial paralysis, bulbar weakness, respiratory failure, pneumonia,[11] and, use of IVIG, anemia, alcohol intake, and history of hypertension.[6] The median time to the onset of hyponatremia in patients with GBS is described to be 8.8 days.[12] However, there are several reports wherein the hyponatremia has preceded GBS[17–20] or the weakness and sodium levels deteriorated in a parallel manner.[21–24]

Sodium homeostasis and normal ADH physiology [Figure 1]

Anti-diuretic hormone [ADH]/arginine vasopressin [AVP] is a peptide hormone produced by hypothalamic magnocellular neurones and carried through its axon to the posterior pituitary, where it is released into the circulation. The major function of ADH is to maintain serum osmolality. The solute particle concentration of a fluid is known as its osmolality. The normal osmolality of human body fluid is 280–295 mOsm/kg and is maintained by ADH, water intake, and renal water transport. The main particle of extracellular fluid [intravascular: interstitiasl: 1:3] that maintains serum osmolality is sodium [Na]. Under physiological circumstances, ADH secretion is linearly stimulated after an increase in serum osmolality greater than 285. Thirst and thus water intake is also activated above 285 mOsm/kg. These are mediated by osmoreceptors and thirst receptors in the hypothalamus and circumventricular organs. Though less sensitive, reduction in intravascular volume [due to reduced intake, renal/ extrarenal losses or third spacing] and fall in blood pressure are also direct stimuli for ADH release and thirst. Hypovolemia shifts the curve to the left and hypervolemia shifts it to right decreasing or increasing the osmotic threshold respectively. Circulating ADH stimulates thirst, causes insertion of water channels in the collecting duct of

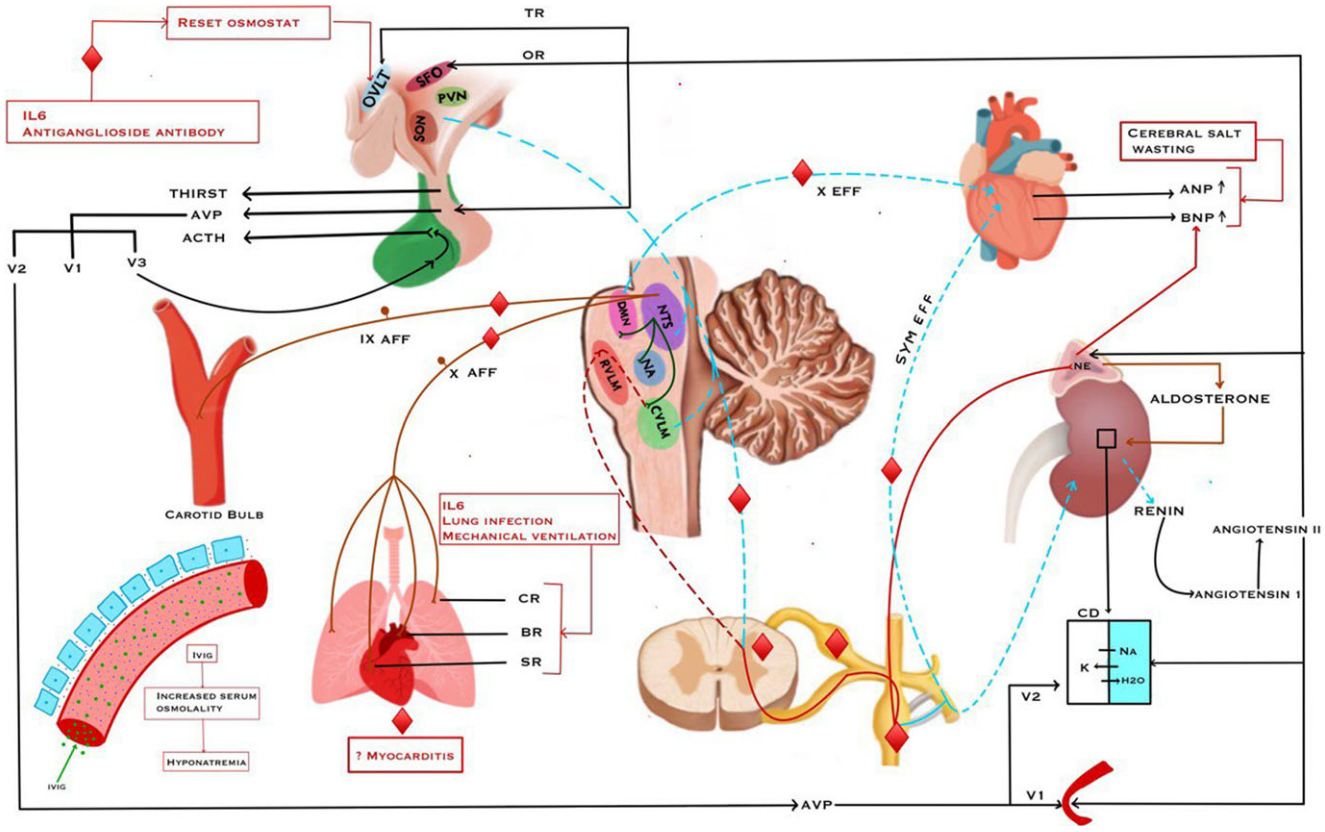

Figure 1: Red boxes indicate the various mechanisms of hyponatremia in GBS patients; red diamonds indicate the sites of autonomic nervous system involvement in GBS. Aff = afferent, Eff- efferent, Ang-angiotensin 1 & 2, BR = baroreceptor; CD = collecting duct; CR = chemoreceptor; CVLM = caudal ventrolateral medulla; DMN = dorsal motor nucleus of vagus; NA = nucleus ambigus; NE = norepinephrine; NTS = nucleus of tractus solitarius; OR osmoreceptor; OVLT organum vasculosum of lamina terminalis; PVN = paraventricular nucleus; RVLM = rostral ventrolateral medulla; SFO = subfornical organ; SO = supraoptic nucleus; V1 V2 V3 vasopressin (ADH)receptors.

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renal tubules leading to water re-absorption and excretion of concentrated urine, helping the body to bring down its osmolality, and acts as a vasoconstrictor to improve the circulatory integrity. The various V1, V2, and V3 receptors located in peripheral vascular smooth muscles, renal tubules, and anterior pituitary mediate the functions of vasoconstriction, renal water re-absorption, and ACTH release, respectively, to maintain fluid and electrolyte homeostasis and arterial circulatory integrity [Figure 1]. The other stimuli for the release of ADH are pain, nausea, angiotensin 2, various lung and central nervous system diseases [ectopic ADH release], interleukin 6 [IL6], serotonin, multiple other drugs etc.[25,26] GBS has multiple factors such as dysautonomia leading to hemodynamic disturbance, pain, nausea, respiratory failure as part of the disease and various subsequent respiratory complications, the presence of IL6 as a post-infectious chemokine in the early phase of the illness, and the use of drugs such as IVIG, pregabalin, carbamazepine, amitriptyline or quinolones that can contribute to the development of the syndrome of inappropriate ADH secretion [SIADH/SIAD].

Etiopathogenesis of low sodium in GBS

The most commonly cited mechanism for hyponatremia in GBS patients is the Syndrome of Inappropriate Anti Diuretic Hormone secretion [SIADH/SIAD]. The others are cerebral salt wasting [CSW], intravenous immune globulin [IVIG], and increased renal salt loss.[27]

Syndrome of inappropriate ADH secretion [SIADH]

GBS being a peripheral nervous system disorder, the most suitable explanation for SIADH seems autonomic neuropathy involving the sympathetic and the parasympathetic nervous system. SIADH is a well-known manifestation of dysautonomia.[5] After the facial nerve, the glossopharyngeal and vagus are the most common cranial nerves involved in GBS that support cardiovascular and hemodynamic autonomic regulation. The various sites of autonomic nervous system [ANS] involvement in patients with GBS according to autopsy studies and through results inferred from autonomic function tests are the afferent and efferent limbs of cardiovascular regulation, the sympathetic chain and ganglia, white rami communicans, vagus, dorsal root ganglia, the spinal nerve origin where motor and sensory roots join and the intermediolateral cell column of the spinal cord[28,29] [Figure 1]. Although there are multiple sites of ANS involvement in GBS, the most common manifestation of tachycardia and hypertension is postulated to be from the demyelination of the afferents of the baroreceptor and cardiopulmonary stretch receptor. This hypothesis has evolved from the observations that proprioceptive loss predicts dysautonomia and afferent limb of cardiovascular regulation has more myelinated fibers than efferent. Normally, baroreceptors are stimulated by the distension of structures in them [eg, increased blood volume/ blood pressure]. The physiological effect of baroreceptor stimulation is inhibition of sympathetic and excitation of the parasympathetic efferents [Figure 1].

Inhibition of the sympathetic efferent results in vasodilatation and hypotension and excitation of the parasympathetic efferent leads to bradycardia. The normal baroreceptor output also maintains an inhibited state of ADH and renin secretion through its connections to the hypothalamus and descending sympathetic tracts [Figure 2A].

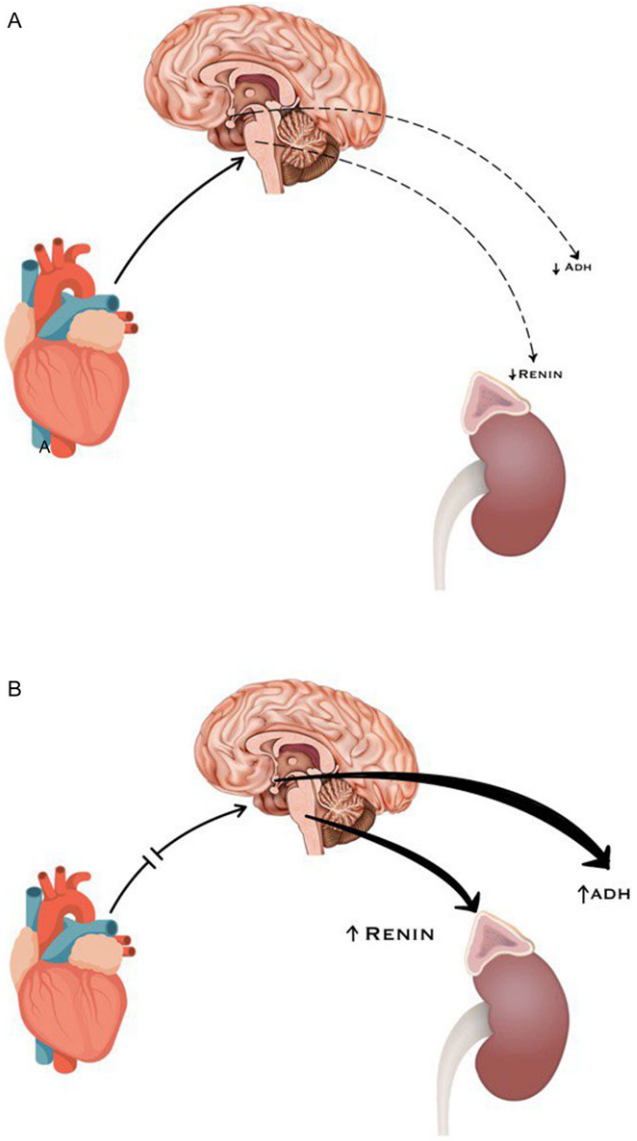

Figure 2: (A) Normal Baroreceptor afferents suppressing renin & ADH secretion. (B) Baroreceptor afferent conduction block leading to excess renin & ADH secretion.

In GBS an afferent conduction block is perceived as low volume state by the baroreceptors causing sympathetic stimulation and parasympathetic inhibition the net effect of which is hypertension, tachycardia, excessive ADH release [SIADH], and renin secretion [Figure 2B]. Renin causes activation of the renin angiotensin aldosterone system [RAAS], which accelerates hypertension and retention of salt and fluid. Angiotensin 2, which is a product of RAAS, is also a potent direct stimulus for the release of ADH from the pituitary as well as the thirst receptors in the circumventricular organs [CVO] [Figure 1]. Development of polydipsia in the context of GBS can contribute to significant sodium abnormalities[30] and virtually can induce the same set of findings produced by SIADH.[31]

Diverse thoracic diseases in these patients like infections and the use of positive pressure ventilation may also precipitate SIADH through abnormalities of the Vagus and sinus reflex afferent mechanism[11,14] [Figure 1]. Autopsy studies showed that myocarditis is a feature of GBS.[29,32] Whether this causes direct damage to baroreceptors/mechano receptors in the atria releasing natriuretic

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factors that act as another source for hyponatremia needs further studies.

Another less-stated pathophysiology is direct stimulation of hypothalamus and pituitary to secrete and release ADH. Patients with GBS and its variants have antiganglioside antibodies which are autoantibodies directed against myelin, axolemma, or nodes of Ranvier.[33] In fact, infusion of the GD2 monoclonal antibody for the treatment of patients with melanoma induced a syndrome of motor sensory polyradiculoneuropathy along with SIADH. Further studies on this GD2 monoclonal antibody led to the discovery that these ganglioside antibodies cross-reacted with not only the peripheral nerve myelin sheath but also the pituitary cytoplasm and hypothalamic osmoreceptors[24,34,35] [Figure 1]. The various autoantibodies released as part of autoimmunity such as anti-GM1, and GD1b may lead to simultaneous demyelination of the peripheral nerve and inflammation of posterior pituitary inducing SIADH manifesting parallel to weakness in a set of these patients[34] [Figure 1].

Recently, Interleukin 6 [IL6] has been implicated in SIADH in patients with GBS. The number of mononuclear cells in the blood increases in the acute phase of the disease. IL6 is an inflammatory cytokine that augments ADH release through two mechanisms. It activates the subfornical organ [SFO] and organum vasculosum of the lamina terminalis [OVLT] and leads to nonosmotic release of ADH and stimulation of thirst.[22] IL6 also causes direct damage to the alveolar basement membrane, leading to activation of hypoxic and pulmonary vasoconstrictor pathway that leads to excessive ADH production[36] [Figure 1]. The reports of hyponatremia of GBS following COVID-19 which is known to mediate excessive cytokine release, reiterate the various mechanisms through which IL6 can cause SIADH.[37,38]

When performing water loading tests in hyponatremic GBS patients during the illness and after complete recovery it was shown that during the illness phase, there is a downward reset of the osmotic threshold for ADH release.[39,40] These patients had an elevated level of ADH and the water load was excreted normally while the plasma remained extremely hypo-osmolar, concluding that osmoregulation was normal but was set abnormally low, possibly due to a disturbance of peripheral volume receptors.[40] This is termed the reset osmostat variety of SIADH.

Cerebral salt wasting syndrome [CSWS]

In a proportion of patients with GBS, especially those associated with dysautonomia, there was a rise in levels of atrial natriuretic peptides [ANP].[41] Later elevated levels of brain natriuretic peptide [BNP] were demonstrated in patients with GBS with dysautonomia.[42] This led to the proposal of salt wasting syndrome as a reason for low sodium. The salt wasting was shown by demonstrating a volume depleted state, a high excreted renal fraction of uric acid, and correction for hyponatremia and high circulating levels of BNP with fluid and electrolyte replenishment. The inappropriate secretion of BNP that is secondary to sympathoadrenal dysfunction as part of dysautonomia is the proposed mechanism [Figure 1]. Further going on to elucidate the source of the natriuretic peptide it was indirectly linked to the adrenal gland by measuring elevated chromogranin levels which is co-localized and co-secreted with the natriuretic peptides [Figure 1]. There is increasing evidence that chromogranin is a marker of cardiac dysfunction.[43] Whether the natriuretic peptide is of adrenal or cardiac origin requires further studies. The hypervolemic state of SIADH may stimulate stretch receptors in atria and ventricle to release natriuretic peptides from the heart, resulting in extravascular shift of fluid and natriuresis.

In conjunction with these association of hyponatremia with sympatho-adrenal dysregulation one should take note of the fact that there are multiple reports where in the hyponatremia has preceded the onset of GBS and also of low sodium levels occurring in GBS patients with absolutely no evidence of dysautonomia, bulbar dysfunction, severe weakness, or respiratory muscle involvement.[18,20,44,45] Hyponatremia has even been proposed to be not due to disease-specific factor in GBS.[10]

Intra venous immunoglobulin [IVIG]

IVIG infusions can cause significant hyponatremia. This can be true hyponatremia or pseudohyponatremia. Pseudohyponatremia is a laboratory artifact due to the high protein delivered to the intravascular compartment. Intravenous infusion of immunoglobulin increases the protein-containing nonaqueous phase of plasma, with a consequent relative decrease in plasma water volume. Since sodium is present only in the aqueous phase, each unit volume of plasma measured has less sodium-containing water, and this is interpreted as hyponatremia[16] which is rather a pseudohyponatremia.[46] When serum protein is above 8 gm/dl, for every 1 gm/dl rise in serum protein, the fall in serum sodium will be about 4.0 mEq/L.[47]

True hyponatremia has also been found to occur after IVIG. This is due to the high concentration of sucrose in the IVIG solution drawing water from the intracellular to extracellular compartment.[48] IVIG was independently associated with a 33% increased likelihood of hyponatremia during hospitalization. The extensive use of IVIG has also been postulated as one of the reasons for the increased incidence of hyponatremia in GBS over the past few decades[6]. However, other studies show that significant alterations in sodium levels cannot completely be explained by use of IVIG alone.[11,49]

Enhanced renal loss of sodium

In a patient with SIAD even in the face of severe hypervolemic hyponatremia there is further natriuresis with hyperosmolar urine. Three factors are invoked to explain this salt loss. (1) Suppression of aldosterone secretion from increased volume of extracellular fluid. (2) Increase in filtered load of sodium due to augmented glomerular filtration rate. (3) Suppression of sodium re-absorption from the proximal tubular in response to expansion of the volume of extracellular fluid volume [so-called 3rd factor].[31]

There is an increased sensitivity of the V2 ADH receptors in the distal tubular and collecting duct, which is responsible for the preference for water over sodium reabsorption despite the hypervolemic state.[9,46] The possibility that an as yet unidentified humoral antidiuretic substance may account for the failure of reduction in urine osmolality has also been proposed.[9,21,31] These observations have led to the belief that increased renal salt loss contributes to hyponatremia.

Apart from these, a variety of factors including the mechanical ventilation itself, pain, drugs [Pregabablin, tricyclic antidepressants, antiepileptics, etc. used for the pain and the antibiotics and antihypertensives] and a reduction in glomerular filtration rate, all probably play a role in producing the defect in water excretion and the resulting overexpansion of body fluids.[26,31]

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Review of cases in literature

Apart from the two case reports,[9,42] the majority of reports in the literature (Table 1) highlight SIADH as the etiology of hyponatremia in GBS patients. The patient reported by Cooper had JE virus infection proven from his throat swab culture. His CSF cell count of 240 cells [all lymphocytes] with a protein of 90 mg makes him an outlier from the typical GBS patient. Headache was reported as a prodromal symptom in him. Whether the neuro-infection contributed to the release of natriuretic peptides and led to CSW rather than SIADH is a point of contention. The case by Lenhardt et al[42] is substantiated to have salt wasting based on high levels of natriuretic peptides and the transient worsening of tachycardia upon instituting fluid restriction and improvement with repletion of fluid electrolytes. The authors mentioned that ADH levels were also high, which contradicts their hypothesis. Natriuretic peptide levels are known to get elevated in SIADH.[50]

Most patients appear to have an antecedent event. Whether antiganglioside antibodies as part of an antecedent infection are causative of the development of SIADH needs further studies. In the few patients who presented with altered sensorium,[18,20,40,46] it is possible that the history of an antecedent infection could not be elicited. This could have been the case with patients who initially presented with non-neurological symptoms such as hypertension[51] or anorexia.[52] The involvement of the cranial nerves in the form of ophthalmoparesis, facial weakness, or bulbar involvement is a common denominator in most cases, with few exceptions.[53] The presence of bulbar dysfunction is a known marker of dysautonomia, since the glossopharyngeal and vagus not only subserve swallowing but also other sympathetic and parasympathetic pathways that control heart rate and blood pressure. Whether involvement of the cranial nerves is always a surrogate marker of dysautonomia needs more studies. The case of a 6-year-old child highlights the lack of involvement of upper extremities or any cranial nerves, but the presentation of hypertension and paraparesis. The biochemical profile demonstrates elevated catecholamines in blood and urine suggestive of sympathetic overactivity, and excessive renin and aldosterone levels which in turn is the stimulus for ADH release.[52]

It is discernible that the etiology of SIADH may differ depending on the timing of hyponatremia in relation to the evolution of GBS. The early hyponatremia that appears in the first one or two weeks of the disease could be a primarily disease-related factor such as coexisting dysautonomia. Lower sodium levels occurring later in the disease course could be secondary to various pulmonary or systemic complication, mechanical ventilation, medications and the dietary variations in a disabled patient. The prognostic and management implications of low sodium could differ depending on the underlying etiology.

The risk of IVIG causing further fall in sodium levels in a hyponatremic patient is another factor to be appreciated. There are reports that highlight on IVIG further worsening sodium levels and in turn the clinical condition and these patients recovering well following Plasma exchange [PLEX].[16,39,54] Future studies are needed before one can conclude that PLEX is preferable to IVIG in a patient of GBS & SIADH.

Some patients with GBS have presented to various medical, surgical, and nephro-urology departments with complaints such as hypertension, abdominal pain, urinary retention/incontinence[19,55,56] that have been treated for urinary tract infection or even with surgeries for acute abdomen.[19] Such patients with low sodium and vague medical complaints seem to have a delay in diagnosis. The symptoms of dysautonomia especially if isolated without sensory motor involvement dissuades the diagnosis most. Whether the clinical criteria for GBS need to be modified to include dysautonomia and low sodium levels as a biochemical marker of the same needs serious consideration. Furthermore, since sodium could be nonspecific, other more specific surrogate markers in blood and urine for dysautonomia need to be explored.

Low sodium is a poor prognostic marker for patients hospitalized for any disease and GBS is no exception. Nevertheless, two factors make hyponatremia in GBS rather distinct. First, its etiology could be disease-related, treatment related, or any of its complications-related, and second, the coexistent autonomic dysfunction makes the treatment with fluid and electrolyte supplementation or restriction very complicated.

Treatment

The appearance of symptoms associated with hyponatremia is strongly linked to rapid evolution with a categorization into mild [130–135], moderate [125–129], and severe [< 125]. A detailed history of the time of symptom onset, current medications, especially antihypertensives diuretics, steroids, neuropathic pain agents, IVIG, etc. Hyponatremic symptoms must be systematically looked for, and absence of the same needs to be documented. Glucose should be measured to rule out hyperglycemia-induced hyponatremia, which may not require sodium correction. Pseudohyponatremia, which is a laboratory phenomenon caused by abnormally high lipid or protein values, can be avoided by measuring sodium using an ion-selective electrode. Acute hyponatremia of < 48 hours with severe or moderately severe symptoms should be treated with 150 ml of 3% saline solution infusion for 20 minutes [Figure 3]. Severe symptoms are defined as vomiting, cardiorespiratory distress, abnormal somnolence, seizures, and coma and moderately severe symptoms as nausea vomiting headache, etc. A rapid increase in sodium of 5 mmols/L is the treatment goal in acute hyponatremia and hence 3% saline infusion can be repeated and sodium needs to be checked every 4 hours. A sodium correction of 8–10 mmol/L/24 hours should not be exceeded.[57] In chronic hyponatremia, patients are less likely to develop neurologic symptoms, but are at high risk of osmotic demyelination. Therefore, the treatment of chronic hyponatremia should be directed toward the reverse/elimination of the underlying cause.[58] Potassium levels give a clue toward diuretic usage adrenal insufficiency, etc. and concomitant correction of potassium in hyponatremic patients may lead to overcorrection and related complications. Ensuring normal thyroid and adrenal functions by measuring thyroid stimulating hormone [TSH] levels and cortisol levels is necessary before diagnosing SIADH.[57] Moreover, distinguishing the syndromes of SIADH and CSW is of utmost importance, as the treatment is entirely different for each [Figure 3].

Sodium and osmolality levels in serum and urine and ADH levels and natriuretic peptide levels are recommended. However, the values could be overlapping and pose difficulty in differentiating SIADH from CSW.[59] The key determinant is the volume status; SIADH is marked by a normal to slightly increased volume status, whereas CSW is a volume-depleted state. Looking for clinical feature [hypotension, dry mucus membranes tachycardia postural hypotension] or laboratory evidences [raised hematocrit, hemoglobin, albumin, Urea] of dehydration helps the clinician at the bedside to a certain extend.[60] However, autonomic dysfunction in these patients may cause confounding signs of tachycardia and

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Table 1: Review of cases of Hyponatremia in GBS reported in literature

Study#	Study	Age & Gender	C/F/GBS variants	AE	DA	MV	Day of HN from onset of illness	Biochemistry	Urine	Treatment	Outcome	Mechanism postulated	Discussion/remarks
1	Fourman P[8] 1958	54 M	Qplegia	NA	NA	Partial support	NA	Na-109	Na-↑ Osm-↑	Water restriction	Died	SiADH	N response to H20 restriction
2	Poyart C[8] 1964	49 NA	Qplegia	NA	NA	Yes	NA	Na-91 Renal-N Adrenal-N	NA		Recovered in 3 months	SIADH	Neg Na balance, ↓free H2O clearance
3	Cooper WC[9] 1965	32 M	Qplegia, bulbar, facial	JE virus infection	NA	Yes	D8-NA	Na-123 Osm 278	Na-NA Osm -↑	IV fluids Na supple H20 restriction	Improved in 6 months	CSW	CSF 240 cells, 90 protein
4	Posner JB[7] 1967 a)	18F	Ataxia, blurred vision, facial, bulbar, Qplegia	URTI + Rash	Yes	Yes	D12-16	Na-105 Osm-247	Na-5 Osm-715 SG-1.025	5%Dextrose Deoxycorticosterone –5 mg Prednisone –60 mg	Improved HS 2 in 44 days	SIADH	
	b)	51F	Qparesis, pneumonia, no facial, no bulbar	Fever Myalgia	NA	Yes	D20-21	Na-114	Na-150 Osm -218 SG-1.002	Steroid 5% NaCl	HIE foll cardiac arrest on Day 20.	SIADH	Low Na after 20 days of respiratory complication Pneumonia/PE
	c)	65F	Qplegia, facial	Fever + Myalgia	NA	Yes	D14-16	Na-118	Na-23 SG-1.010	ACTH 40mg IV fluids	Cardiac arrest	SiADH	Pneumonia at admission
	d)	36F	Paresthesias, oparesis, facial	Doubtful	NA	No	D10-13	Na-116	Na 289 Osm-732 SG-1019	5% NaCl-300ml	HS-2 in 4.5 months	SIADH	
5	Davies AG[7] 1971 a)	63 F	Qplegia, facial & bulbar	URTI	Yes	Yes	NA	Na-127		Fluid restriction	Off MV D14	SIADH	Pos fluid balance with pulmonary oedema
	4 other cases	NA	Qplegia bulbar +	NA	NA	Yes	NA	<130 in all Osm -<260 in all		NA	All recovered	SIADH	Oedema & Vagus invt in all suggesting AD Normal intake of water in GBS pts may prove fatal
6	Penny MD[40] 1979	51 M	Qparesis, urinary retention, confusion	No	Yes	No	D7-	Na-125@adm 110 Osm-253	Na-35 Osm-273	3% saline, Fluid restriction to 1L/d	Improved	SIADH Reset osmostat variety	Na load natriuresis & H2O load aquaresis despite ↓ Na & ↓ serum Osm
7	Hochman[44] 1982	62 M	Paraparesis	URTI	Absent	No	D-4 to D9	Na 114 Osm 260	Na-56 Osm-674	Fluid restriction 3% saline	Improved	SIADH	Factors other than vagal inhibitory action may cause SIADH
8	Kaneko K[52] 1989	6 M	Paraparesis, headache, anorexia, no UL/Facial/Bulbar	No	Yes	No	D5-16	Na-129 Epi/NE/ renin/Angio1 & 2-↑ ADH-↑ Osm -258	Osm 496 Epi/NE -↑	None	Improved in 4 weeks to HS 0	SIADH	Sympathetic overactivity other than vagal dysfunction can lead to SIADH
9	Ramaprasad ST[45] 1995	55 F	Bulbar, ataxia, ophthalmoparesis	URTI with conjunctivitis	Present	No	D3-D6 of adm	Na-108 Osm-236 Uric acid 1.3	Osm-636	Furosimide 3% saline Fluid restriction	recovered	SIADH/atrial natriuretic hormone	MFS variant

10	Cooke CR[39] 1998	54 M	Qplegia, ophthalmo-paresis	Herpes Zoster	Yes	No	D11->1 30days	Na 118 Osm 256	Na 49 Osm-745	PLEX frusimide 0.9%saline	recovered	NAADH independent mechanism NASIADH humoral ADH like substance	B/L Pneumonia ↑sensitivity of renal tubules to ADH
11	Lawn N[16] 1998	49F	Typical GBS	NA	NA	No	D4-NA	Na-122	Na-45 Osm-474	IVIGx5d days PLEX-D6	recovered	Pseudo HN due to IVIG	Na normalized with PLEX
12	Hoffman O[17] 1999	38 F	HN, GBS 3 days later	NA	No		D–3 to NA					SIADH	
13	Inoue[22] 2010	73 M	Qparesis, no bulbar	Yes	No	No	D2-D15	Na 106 Osm-221 ADH -↑ Renin -↓	Na-56 Osm-416	0.9% saline water restriction	Recovered in 2 weeks	SIADH	↓renin & AT due to SIADH
14	Ramanathan S[23]	82 F	Initial DA + HN, sensory motor AIDP 6 days later + facial	URTI	Yes	No	D-7-NA	Na-122 Osm 268	Na 56 Osm-553	Fluid restriction IVIGx5d	Recovered HS-3 by 5 weeks	SIADH	
15	Lenhard T[42] 2010	69 F	Qparesis, HN	EBV	Yes	No	D8-21	Na-122 AVP-↑ BNP-↑ GM1&GM2-IgM +	NA	NaCl tablets 0.9% saline IVIG		Cerebral/ renal salt wasting	AIDP
16	Vasquez TM[24] 2011	63 M	Paresthesia, ataxia, qparesi, facial & bulbar	Fever + diarrhea	NA	NA	NA	Na-120 Osm-259	Na-144 Osm-719	NA	NA	SIADH	↓Na & GBS at admission
17	Kloesel B[18] 2013	62 F	COPD, Coma @ adm, GBS 6 days later	NA	NA	No	D-5- (Low Na Prior to GBS by 5 days)	Na-110 Osm-235	Na-76 Osm-413	3% saline NaCl-tablets Fluid restriction IVIG	recovered5 months	SIADH+ pseudo HN	Thiazide many years for HTN but Na 3 months prior was normal
18	Cakyrgoz MY[19] 2013	44 M	Lap chole, low Na-postop D2, GBS with facial, bulbar, ophthalmo-paresis	URTI	Yes	No	D–1-NA	Na-120 Osm-240	Na-89 Osm-515	Fluid restriction 3% Saline Furosemide IVIGx5d	improved	SIADH	Ulcerative colitis in past
19	Wankar A[46] 2014	60 F	Drowsy, oparesis, facial, bulbar	NA	NA	No	D5-13	Na-113	Na-112	IVIG Fluid restriction, 3%saline	Improved HS-2 in 2 weeks	SIADH	HN simultaneous as GBS
20	Srisung W[53] 2015	36 M	AMSAN, no facial, no bulbar	NO	NA	No	6 weeks	Na 115 Osm-234	Na <20 SG 1.045	IVIG- 2 course NS Fluid restriction Tolvaptan	Na-improved in few days	SIADH	Urine Osm -after NS-531
21	James J[20] 2017	47 M	Seizures, paraparesis D10, no facial, NO bulbar	Febrile illness	NA	No	D-10 - D15	Na-106 Cortisol & thyroid - normal	Na-55 Osm-572 PBG-neg	IVIG, Tolvaptan Fluid restriction	improved	SIADH	

(*Continued*)

Table 1: (*Continued*)

Study#	Study	Age & Gender	C/F/GBS variants	AE	DA	MV	Day of HN from onset of illness	Biochemistry	Urine	Treatment	Outcome	Mechanism postulated	Discussion/remarks
22	Zemke AM[21] 2018	51 M	Qparesis	URTI	Yes	No	D4-NA	Na 128 Osm-Low TSH-N	Osm-↑	IVIG Fluid restriction IV fluids	improved	SIADH	HTN & Hypothyroid on Treatment
23	Asti D[54] 2018	72 F	Paraparesis, paresthesia	No	Yes	No		Na-113 Osm-245	Osm-702	0.9% saline 3% Saline Fluid restriction Tolvaptan PLEX-5 Cycles	Recovered with PLEX	SIADH	Diagnosis of UTI-2 days prior Dysautonomia
28	Shah PM[55] 2019	56 F	Fluctuating HTN, Low back ache, AIDP-D8	No	Yes	Yes	D—1-14	Na-107 K-2.5 Osm-285	Osm-577	3% saline PLEX	Recovered	NA	
29	Vega JE[56] 2020	59 F	Paresthesia, paraparesis, bladder incontinenece	Diarrhoea	NA	No	NA	Na-126 Osm-239	Osm-591 Na-80	IVIG 3% saline H2O-restriction Tolvaptan	recovered	SIADH	DM
24	Griffin D[30] 2020	57 F	Qparesis, ataxia, paresthesia	URTI	NA	No	D8-NA	Na-116 Osm-241	Na->40	IVIG 3% Saline	NA	SIADH	Switched to IVIG after detection of HN
25	Mario GC[37] 2020	63 F	Paraparesis, facial & ophthalmoparesis	Covid 19	NA	No	D3-NA	Na-132	NA	IVIGx 5 days	Improved	SIADH	CXR- no covid pneumonia NATRF with 2nd adm & MV in a month
26	Maffi G[51] 2021	68 F	HTN-2 wks, paresth-4 days, facial + Qparesis-10 days later	NA	Yes	No	D—10–NA	Na-115 ACTH & Cortisol-normal	NA	3% Saline IVIG	improved	SIADH	Presented with DA (resistant HTN) & HN
27	Fujiwara S[34] 2021	72 F	Ataxia diplopia, no facial/bulbar	Respiratory	NA	NA	D8-27	Na-119 Osm-254 GD1b,GQ1b, GT1a IgM + Gal C IgM+ AVP-N	Na-73 Osm-457	IVIG 0.9% saline Fluid restriction	Recovered in 4 weeks	SIADH	MFS variant ↑ antibodies pathogenic to SIADH
30	Santoro[38] 2021	47 M	AIDP	No	Yes	No		Na-102		IVIG H2O restriction 3% saline Tolvaptan	Improved in 2 weeks	SIADH	

ADH = antidiuretic hormone; Adm = admission; ACTH = adreno corticotropic hormone; AE = antecedent event; AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMSAN = acute motor sensory axonal neuropathy; AT = angiotensin; B/L = bilateral; BNP = brain natriuretic peptide; C/F = clinical features; Lap Chole = laparoscopic cholecystectomy; D = day from onset of GBS; DA = dysautonomia; Foll = following; GBS = Guillian Barre Syndrome; HIE = hypoxic ischemic encephalopathy; HN = hyponatremia; HTN = hypertension; H20 = water; HS = Hughes scale; IV = intravenous; IVIG = intravenous immune globulin; JE = Japanese Encephalitis; MFS = Miller fischer syndrome; AD = autonomiac dysfunction; MV = mechanical ventilation; Na = sodium; NaCl = sodium chloride; NA = data not available; NE = norepinephrine; Neg = negative; Nl = normal; No = number; NS = normal saline; Osm = osmolality; PE = pulmonary embolism; PLEX = plasma exchange; Pneum = pneumonia; Pos = positive; Qplegia/Q paresis = Quadriplegia/Quadropareis; SG = specific gravity; SIADH = syndrome of inappropriate antidiuretic hormone secretion; Symp = sympathetic; TSH = thyroid stimulating hormaone; TRF = treatment related fluctuation; UL = upper limb; URTI = upper respiratory tract infection; Var = variation; + = present.

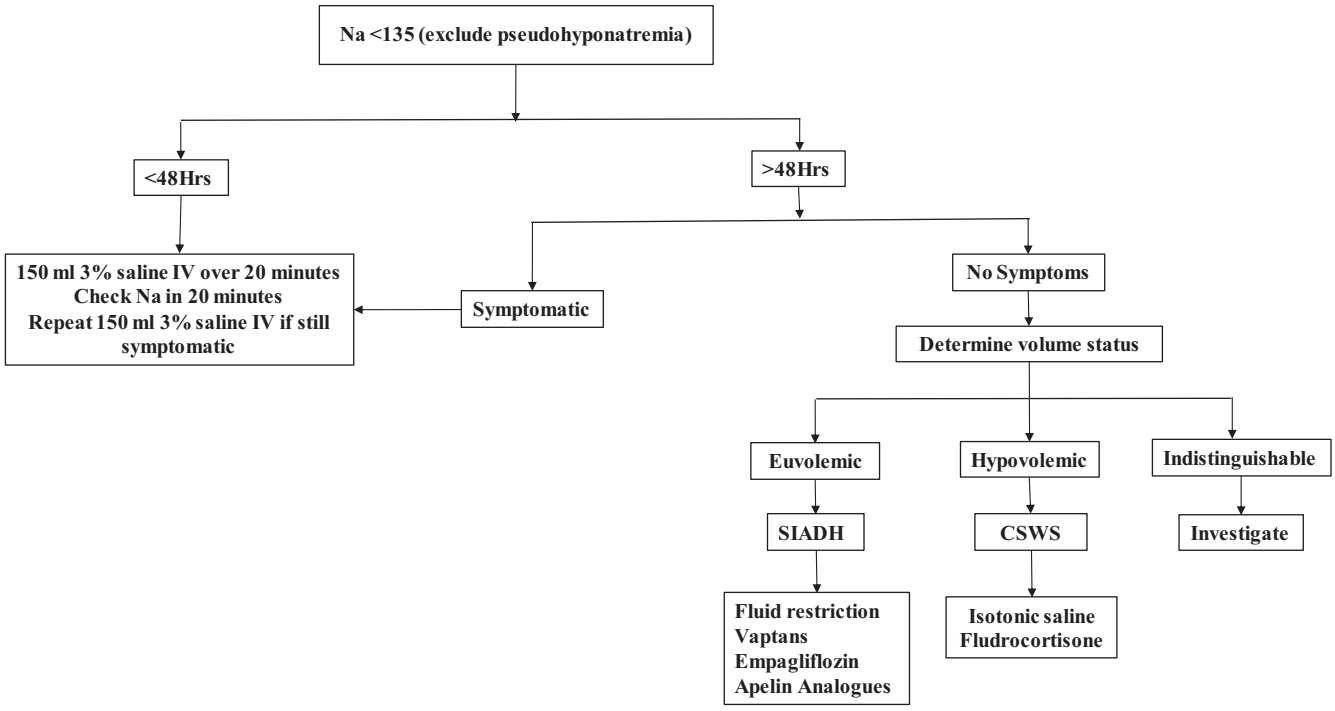

Figure 3: Approach to hyponatremia in GBS. Details of investigations elaborated in text. CSWS = cerebral salt wasting syndrome; Na = Sodium; SIADH = syndrome of inappropriate ADH secretion.

hypotension, etc. Inserting a central venous pressure monitor system provides a less ambiguous assessment of the patient.[61]

Since all symptoms and effects of SIADH are due to excess water retention causing dilutional hyponatremia the cornerstone of treatment is water restriction in them.[3,31,57,58] In refractory cases, vasopressin antagonists especially of the V2 receptor [Vaptans] are another option for inducing aquaresis and thereby correcting sodium. Though there is a concern about overcorrection of hyponatremia lower doses of tolvaptan [7·5 mg/day] are found to be efficacious and safer.[58] Sodium glucose cotransporter -2 inhibtors [SGLT-2i] like Empagliflozin which is primarily used as an antidiabetic agent and Apelin analogs which is a central inhibitor of ADH release are some of the newer agents which may have a potential role in treatment of SIADH pending appropriate clinical trials.

On the contrary, the first line of management for CSW is fluid and electrolyte repletion. In refractory cases, fludrocortisone seems to effectively control natriuresis [class2].[3,60]

Conclusion

Of the multiple in-hospital complications of GBS, hyponatremia is one of the modifiable prognostic factors which can be easily recognized and corrected. Most studies do not include sodium estimation, and the available studies do not mention serial values during the course of GBS, thus underestimating the exact incidence, prevalence, and magnitude of the problem.

Hyponatremia in GBS is multifactorial, but only a few case reports have tried to explore its mechanism, and much needs to be known. Hyponatremia can occasionally precede motor weakness and manifest itself with systemic symptoms, probably due to early-onset dysautonomia. Low sodium can influence or confound the clinical course and outcome of GBS. Close monitoring of patients with high risk for hyponatremia [recognized predictors] may help in early detection. Early and appropriate intervention for low sodium may reduce the morbidity and mortality in GBS patients.

Search strategy

References for this review was identified by searches of pubmed and google upto December 2022 and references from relevant article. The search terms “Guillain Barre syndrome”, “Hyponatremia”, “SIADH”, “Cerebral salt wasting”, were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered.

Author contributions. ANB – Contributed to intellectual content, conceptualization, design of work, writing of manuscript, collection of literature, conceptualization of diagrams and algorithms, proofreading and correction, critical feedback, correction of language, and helped shape the final format.

NC – Assisted In the collection of literature, formatting, and drawing of diagrams and algorithms, conceptualization of diagrams and algorithms, and helped shape the final format.

SSK – Contributed to the collection of literature, provided critical feedback, and assisted in shaping the final format.

ABT – Contributed to the intellectual content/conceptualization, proofreading and correction, correction of language, provided critical feedback, and helped shape into the final format.

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