Clin Pediatr Endocrinol 2017; 26(4), 197–205

Review

Characteristic clinical features of adipsic hypernatremia patients with subfornical organ-targeting antibody

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Abstract. Adipsic hypernatremia is a rare disease presenting as persistent hypernatremia with disturbance of thirst regulation and hypothalamic dysfunction. As a result of congenital disease, tumors, or inflammation, most cases are accompanied by structural abnormalities in the hypothalamic-pituitary area. While cases with no hypothalamic-pituitary structural lesion have been reported, their etiology has not been elucidated. Recently, we reported three patients with adipsic hypernatremia whose serum-derived immunoglobulin (Ig) specifically reacted with mouse subfornical organ (SFO) tissue. As one of the circumventricular organs (CVOs) that form a sensory interface between the blood and brain, the SFO is a critical site for generating physiological responses to dehydration and hypernatremia. Intravenous injection of the patient's Ig fraction induced hypernatremia in mice, along with inflammation and apoptosis in the SFO. These results support a new autoimmunity-related mechanism for inducing adipsic hypernatremia without demonstrable hypothalamic-pituitary structural lesions. In this review, we aim to highlight the characteristic clinical features of these patients, in addition to etiological mechanisms related to SFO function. These findings may be useful for diagnosing adipsic hypernatremia caused by an autoimmune response to the SFO, and support development of new strategies for prevention and treatment.

Key words: adipsic hypernatremia, subfornical organ, sensory circumventricular organs, hypothalamus dysfunction

Introduction

Sodium levels in body fluids are strictly controlled by water/salt intake and urinary excretion. Body fluids are therefore constantly monitored by osmolality or sodium level sensors in the brain, which control thirst sensation, preference for salt, and AVP (1, 2). In normal subjects, approximately 280 mOsm/kg H_2O is considered the osmotic threshold for the release

Received: November 6, 2016
Accepted: April 15, 2017
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of AVP (3).

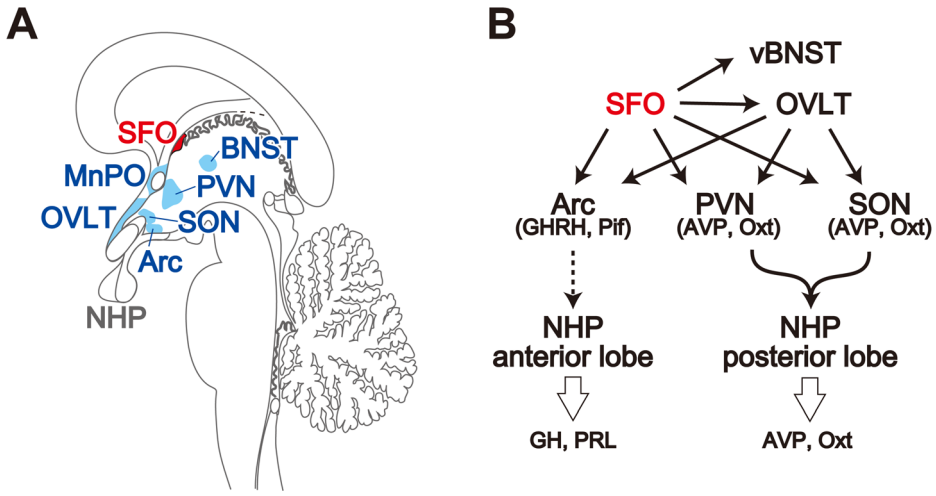
Adipsic hypernatremia is clinically characterized by an increase of both the osmotic set point for AVP release, and the threshold for thirst perception, resulting in persistent hypernatremia with a euvolemic state (4–6). As a result of congenital disease, tumors, or inflammation, most cases are accompanied by structural abnormalities in the hypothalamic-pituitary area; however, cases with no structural lesion have also been reported since the 1970s (7–12). Some of these cases exhibited hypopituitarism including GH deficiency (GHD), rapid obesity, and autonomic failure. These patients generally had a poor prognosis, often due to respiratory failure, such as apnea. Although almost 50 years have passed, the underlying mechanisms for this condition have yet to be clearly elucidated.

In 2010, Hiyama *et al.* reported a case in which autoantibodies targeting the sensory circumventricular organs (sCVOs) caused adipsic hypernatremia without hypothalamic-pituitary lesions, demonstrable by magnetic resonance imaging (MRI) (13). The patient's serum contained autoantibodies to Na_x, the brain Na^+-level sensor, and immunostaining of mouse brain sections revealed that sensory circumventricular organs (sCVOs), including the subfornical organ (SFO), were specifically stained with the patient's serum. Passive transfer of the immunoglobulin (Ig) fraction of the patient's serum reproduced her symptoms in mice, with abnormal reductions in water intake and AVP-release, most likely due to complement-mediated cell death in the sCVOs where Na_x is expressed. These results suggest a new etiology for adipsic hypernatremia caused by autoimmune responses. Additionally, we recently reported that the serum of three patients, exhibiting adipsic hypernatremia without demonstrable hypothalamus-pituitary lesion, reacted with a mouse SFO, though their sera did not contain anti-Na_x antibodies (14). Mice injected with a patient's Ig exhibited similar pathophysiology as the patient, including hypernatremia and defects in thirst sensation and AVP release. Intriguingly, there were similar clinical features among four patients, likely resulting from specific immune responses to the SFO. In this review, we summarized the clinical characteristics of those patients with adipsic hypernatremia to highlight common findings, which might have resulted from SFO damage.

Interaction with Other Nuclei and Peptides in the SFO

Three CVOs form a sensory interface between the blood and brain: the SFO, OVLT and area postrema. All lack a blood-brain barrier and contain receptors for many substances that circulate in the blood (15). Among the CVOs, the SFO protrudes ventrally from the fornix into the third ventricle, just caudal to the foramen of Monroe at the confluence of the lateral and third ventricles (16). The core of the SFO is positioned to be permeated by blood-borne, low-molecular-weight molecules, such as angiotensin II (Ang II). The peripheral portion, however, is positioned to respond to factors in cerebrospinal fluid (CSF), such as sodium (17). Na^+-levels in body fluids are sensed by Na_x channels expressed in specific glial cells in the SFO (18–20). Activation of Na_x stimulates glial cells to release lactate, which functions as a gliotransmitter and activates GABAergic inhibitory neurons in the SFO (21).

The SFO is a unique nucleus in that its afferent and efferent projections are well placed to respond to blood-borne signals and integrate them with neuronal signals (16). The SFO extends efferent axonal projections to the median preoptic nucleus (MnPO), OVLT, supraoptic nucleus (SON), arcuate nucleus (ARC), lateral preoptic area, and lateral hypothalamus (Fig. 1) (16, 22–25). A small portion of SFO neurons in the periphery extend collateral projections to both the MnPO and the paraventricular nucleus of the hypothalamus (PVN), likely affecting the AVP system (26). In addition, neurons in the core portion of the SFO also project to the



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Oringins of afferent inputs to SFO	Targets of efferent outputs from SFO
Medial septal nucleus, locus coeruleus, lateral parabrachial nucleus, substantia innominata, nucleus of the solitary tract, etc.	OVLT, vBNST, MnPO, PVN, SON, Arc, lateral preoptic area, lateral hypothalamus periventricular nucleus, median preoptic nucleus, etc.

Fig. 1. Neural connections of the subfornical organ (SFO). A: Median sagittal section through the human brain showing the SFO (red) and its efferent terminal fields (blue). B: Schematic overview of neural circuits originating from the SFO. Closed arrows indicate direct (solid line) and indirect (dotted line) neural connections. Open arrows indicate release of peptides to the circulation. SFO neurons projecting to the vBNST encode salt appetite, whereas those to the OVLT encode thirst sensations (29). C: Table showing the nuclei that have afferent and efferent neuronal connections with SFO. OVLT, organum vasculosum of the lamina terminalis; SON, supraoptic nucleus; PVN, paraventricular nucleus of the hypothalamus; MnPO, median preoptic nucleus; vBNST, ventral part of bed nucleus of the stria terminalis; NH, neurohypophysis; Arc, arcuate nucleus; GHRH, GH releasing hormone; Pif, prolactin inhibitory factor (dopamine); AVP, Arginine vasopressin; Oxy, oxytocin. Figure A is modified from (40).

parvocellular PVN (pPVN), which synthesizes corticotropin-releasing hormone, and the basal nucleus of the stria terminalis (27).

The renin-angiotensin-aldosterone system (RAAS) is an important regulator of fluid balance (16). Intracranial injection of Ang II causes increased water and salt intake (28). AT1a-positive SFO neurons projecting to the OVLT and vBNST encode thirst and salt appetite, respectively; neuronal groups were named 'water neurons' and 'salt neurons', respectively (29). $[Na^+]$ elevation in the blood stream activates Na_x in the SFO to suppress the activity of salt neurons through activation of GABAergic inhibitory neurons. In contrast, cholecystokinin, which increases in the SFO

under Na^+-depleted conditions, suppresses the activity of water neurons by activating a distinct group of GABAergic inhibitory neurons.

Orexigens and anorexigens both act at the SFO, but via different neuronal pathways (30). Some experimental evidence suggests ghrelin may play a role in regulation of energy balance by action at the SFO (31). Administration of ghrelin has been clearly demonstrated to stimulate feeding and adiposity in mice and rats (32). Collectively, the SFO is a specialized organ for regulating thirst and energy balance, mediated by peptides such as Ang II and ghrelin in blood and CSF.

Clinical Features of Patients Exhibiting Adipsic Hypernatremia with Antibodies Targeting SFO

Clinical findings of patients with adipsic hypernatremia, with (33) and without (13, 14) structural lesions, are compared and summarized in Tables 1 and 2. In patients developing adipsic hypernatremia caused by congenital abnormalities, such as septo-optic dysplasia, clinical characteristics often present as neurodevelopmental delay, seizures, thermal dysregulation, and anterior pituitary dysfunction [defects in the release control of GH, thyroid stimulating hormone (TSH), and ACTH] (33). These patients typically have Langerhans histiocytosis and teratoma in the hypothalamus. In addition to thermal dysfunction, these patients can present with obesity or leanness (5). Their prognosis was reported to be poor.

Additionally, reports of patients exhibiting rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation (ROHHAD), and ROHHAD with neural tumor syndrome (ROHHADNET), indicate that these diseases often co-occur with adipsic hypernatremia (34). In all such cases, alveolar hypoventilation was observed; notably, hypothalamic dysfunction, such as ophthalmologic manifestations and thermal dysregulation, frequently occurred in these patients. In contrast, patients with SFO-reactive antibodies did not exhibit hypoventilation or thermal dysregulation.

Common Clinical Symptoms and Findings among Cases with Antibody to SFO

In summary, the common syndromes at clinical onset among the four patients with SFO-reactive antibodies: A) hypernatremia without thirst sensation; B) impaired AVP release; C) lack of structural aberrance in the hypothalamus-pituitary region; D) childhood onset; E) obesity; F) increased serum PRL; G) impairment of GH release; H) increased plasma renin-activity; and I) intact urine-concentrating capacity. The specific details and mechanism of each feature are described here:

(A, B) A deficiency in AVP secretion in response to serum hyperosmolality was observed in all cases. Impaired secretion of AVP associated with adipsia was considered a direct cause of persistent hypernatremia, which led us to diagnose patients with adipsic hypernatremia. Although a patient's serum osmolality was higher than 300 mOsm/l during a water-restriction test, she did not feel consistently thirsty. MRI results showed a clearly detectable posterior pituitary gland with local presence of secretory granules, suggesting preservation of AVP synthesis.

(C) These symptoms and findings likely result from cellular damage in the SFO induced by the patient's immune response. However, structural abnormalities were not detected in the hypothalamus-pituitary area by MRI in any of these cases. Damage incurred in the SFO, resulting from an immune response, might be too slight to be detected by MRI analyses, as the SFO is ten times smaller than the posterior lobe of the pituitary.

(D) We have not experienced any adult-onset cases so far. We speculate that some immature immune response to inflammation, triggered by infection, may underlie the autoimmune reaction

Table 1 Summary of clinical characteristics of patients with or without antibody targeting the subfornical organ area

	With antibody targeting the SFO but not anti-Na_x antibody (n = 3) (14)	With anti-Na_x antibody (n = 1) (13)	With congenital abnormalities in hypothalamus pituitary lesion (n = 7) (32)	With tumors in hypothalamus pituitary lesion (n = 3) (5)
Underlying diagnosis	None (2/3)	Ganglioneuroma	Optic nerve hypoplasia: 2 Septo-optic dysplasia: 1 Semi lobar holoprosencephaly: 1 Structural hypothalamic pituitary abnormalities: 3	Histiocytosis: 2 Teratoma: 1
Average age at diagnosis	5 yr old (3–8 yr old)	6.5 yr old	24 d old (3 d–3 mo old)	20 yr old (12–26 yr old)
Obesity during follow-up period	3/3 (average BMI at first visit = 27 (25.8~29.2)	1/1 (BMI at first visit = 22.4)	3/7	2/3
Neuro-developmental delay	None	None	5/7	1/3
Seizure	None	None	4/7	None
Thermal dysfunction	None	None	5/7	1/3

Table 2 Results of endocrinological findings in patients with or without antibody targeting the subfornical organ area

	With antibody targeting the SFO but not anti-Na_x antibody (n = 3) (14)	With anti-Na_x antibody (n = 1) (13)	With congenital abnormalities in hypothalamus pituitary lesion (n = 7) (32)	With tumors in hypothalamus pituitary lesion (n = 3) (5)
Anterior pituitary dysfunction	GH (3/3) TSH (1/3) Precocious puberty (2/3)	None	GH (6/7) TSH (6/7) ACTH (5/7) LH-FSH (2/7)	GH (2/3) TSH (2/3) ACTH (1/3)
Other clinical examination findings	Hyperprolactinemia Increased plasma renin activity	Hyperprolactinemia Increased plasma renin activity Hypokalemia Increased aldolase	None had hyperprolactinemia	Hyperlipidemia (3/3)

in childhood. Consistent with this view, some patients experienced episodic inflammation with infections such as influenza virus and opsoclonus myoclonus syndrome (OMS), a feature often associated with neuroblastic tumors. Similar cases of autoimmune reactions in childhood have been reported (35, 36); for instance, development of childhood-onset narcolepsy has been reported following influenza A infection and vaccination, and is caused by an autoimmune response related to autoantibodies to neuropeptide glutamic acid-isoleucine/α-melanocyte-stimulating hormone (NEI/αMSH) and cytotoxic T cell response.

(E) All patients presented with rapidly progressing obesity during the onset period. As they did not show overeating, we believe the obesity may result from a disorder of energy balance. Although we have not determined the cause of the metabolic disorder, ghrelin signaling is a plausible target as it affects energy balance via SFO. More detailed studies, including measurements of ghrelin levels in patients' sera, would be required.

(F) It is well known that PRL release is controlled by PRL-inhibiting factors, such as dopamine produced in the ARC (37). Since the SFO has efferent projections to the ARC (18), it is conceivable that damage to the SFO might reduce dopamine release from neurons in the ARC.

(G) It is well known that GHD is associated with obesity (38). However, our patient still showed severe GHD even after normalization of her BMI and hypothyroidism. GH-secretagogue receptor (GHS-R), a receptor for ghrelin, known to evoke the release of GH via a GHRH-independent pathway, is expressed in the SFO (31, 39). The SFO subpopulation of neurons is consistently, dose-dependently excited by application of exogenous ghrelin (31), suggesting that SFO damage might have caused defects in GH release.

(H, I) Increased plasma renin activity (PRA) was also detected in all patients. As mentioned above, Ang II stimulates thirst *via* water neurons in the SFO (29), suggesting that cellular damage in the SFO induces a secondary increase of PRA in the blood to compensate for sensitivity within the SFO.

Precocious puberty was observed in some cases, and damage in the SFO may also underlie these symptoms. Precocious puberty might be caused by hyperactivity of LH releasing hormone (LHRH) neurons in the preoptic area, which also receives efferent projections from the SFO. More detailed analyses, including measurement of LHRH levels in patients' sera, is still required.

Future Directions

There are still two unresolved points related to the pathophysiology of this disorder: the antigen eliciting the specific immune response to SFO, and the mechanism for producing this antibody. We attempted to identify the specific antigens of the autoantibodies in the three patients, but all attempts failed, suggesting that these antigen molecules are not abundant in the SFO (14). Nevertheless, immunohistochemistry using patients' sera suggested that the antigen molecule is expressed specifically in the SFO area, but not other brain tissue. Identification of molecules specific to the SFO will be the subject of future investigation.

Generally, the incident prompting the onset of an autoimmune disorder is thought to be inflammation triggered by tumors and infections in subjects with preexisting susceptibilities. Injection of patient Ig into mice led to complement deposition, infiltration of inflammatory cells, and damage to the mouse SFO area resulting from apoptosis (14, 16). The classical complement pathway is activated by the interaction of an antigen-antibody complex with a C1 component on the cell-surface target. Once this pathway is evoked in the SFO, it is believed to permanently damage the SFO by inducing apoptosis. Similar damage was noted in the SFO of the patients. New strategies to prevent specific inflammatory conditions would be required to treat these patients; a trial to reduce or eliminate patient

autoantibodies deserves consideration. Strategies may include autoantibody elimination by double-filtration plasmapheresis or immunoadsorption therapy, as well as the administration of steroids, immunosuppressants, or rituximab (anti-CD20 antibody). Careful monitoring of adverse events, and approval by the appropriate ethics committees, would be mandatory. In the future, more detailed mechanisms and clinical findings will aid development and selection of new clinical strategies.

Conclusion

Adipsic hypernatremia patients with specific immune responses to SFO display common clinical features. The SFO is a specialized area controlling thirst and salt appetite, as well as several neurosecretory systems with neural connections to other brain nuclei and receptors for circulating peptides. SFO damage by autoimmune response is thought to induce a variety of symptoms, including loss of thirst sensation, hypernatremia, obesity, GHD, and a number of others. It is possible that immunohistochemistry of mouse brain using patients' sera could be used to diagnose patients with autoimmune diseases accompanied by adipsic hypernatremia without demonstrable hypothalamic lesions.

Acknowledgements

This work was supported by the Japanese Society for Pediatric Endocrinology Future Development Grant sponsored by Novo Nordisk Pharma, Ltd. We are grateful to Drs. Eiji Watanabe, Masahito Matsumoto, Akihiro Fujikawa, and Lin Chia-Hao (NIBB) for their analyses. We are also grateful to Shinichi Matsuda, Hiroshi Kajiwara, and Fumio Niimura (Tokai University School of Medicine); Drs. Keiichi Hara (Kure Medical Center), Reiko Kagawa, and Sonoko Sakata (Hiroshima University Hospital), Mayumi Ishikawa, Hideo Cho, and Makoto Anzo (Kawasaki Municipal Hospital), Shinobu Takayasu, Takeshi Nigawara, Makoto Daimon, Tomihiko Sato, Kiminori Terui, and Etsuro Ito (Hirosaki University Graduate School of Medicine) for their cooperation in providing serum samples and clinical information.

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