Neuro-psycho disorders and Hyponatremia in a Renal Carcinoma patient revealed as Anti-LGI1 Encephalitis and Renal Salt Wasting: a Case Report

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Case report

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Abstract

Background: LGI1 (leucine-rich anti-glioma 1 protein) is one of the latest identified voltage-gated potassium channels related antigens. Anti-LGI1 encephalitis affected the limbic systems presenting with subacute onset of progressive neurological, cognitive, psychiatric disturbance and life threatening obstinate hyponatremia. However, Anti-LGI1 encephalitis was mostly considered to be non-malignancy related. The hyponatremia mechanism remains to be elusive. **Case presentation:** Here we firstly report a 71-year-old female diagnosed of anti-LGI1 encephalitis after renal clear cell carcinoma resection. The old female discovered a renal mass which was identified as renal clear cell carcinoma. Two months after the renal carcinoma resection, the patient fell down frequently and showed discontinuous neuro-psychiatric disorders manifested as memory decline, disorientation, and unintentional upper limb movements as typical faciobrachial dystonic seizure episode. She also had hyponatremia. The combination of her clinical presentations and laboratory assessments supported a diagnosis of anti-LGI1 encephalitis and renal salt wasting. The Immunohistochemistry studies of the kidney resection indicated circulating LGI1 antibodies in sera might be binding to extracellular LGI1 predominantly in the proximal tubule where the major defect in solute transport exists in renal salt wasting. **Conclusion:** Anti-LGI1 encephalitis with renal carcinoma indicated its paralimbic pathology origin. The early diagnosis and immune-modulation therapy could lead to good outcome. The hyponatremia in anti-LGI1 encephalitis was renal salt wasting instead of syndrome of inappropriate secretion of antidiuretic hormone.

Background

Anti-LGI1 encephalitis affects the limbic systems and presents with subacute onset of progressive neurological, cognitive, psychiatric disturbance and obstinate hyponatremia [1, 2]. Anti-LGI1 encephalitis is mostly considered to be non-malignancy related [3, 4]. We reported a case of anti-LGI1 encephalitis presented cognitive disorder and FBDS (faciobrachial dystonic seizure) after resection of her renal carcinoma for the first time. The unique relationship between serum sodium and fractional excretion of uric acid FE_{urate} (fractional excretion of uric acid) determined that the hyponatremia was due to CRSW (cerebral/renal salt wasting) or more appropriately RSW (renal salt wasting) instead of the SIADH (syndrome of inappropriate secretion of antidiuretic hormone). The IHC (Immunohistochemistry) studies of the kidney indicated that circulating LGI1 antibodies in sera might be binding to extracellular LGI1 predominantly in the proximal tubule where the major defect in solute transport exists in RSW.

Case Presentation

A 71 years old female was found to have a renal mass which was pathologically identified as renal clear carcinoma that was surgically removed. Almost two months after surgery the patient was noted to be hyponatremic and complained of fatigue. She also fell down frequently, and reported unintentional upper limb movements and unstable gait. Her family also noticed cognitive defects in patient. The patient showed decline in short term memory, inability to recognize family members and being unaware of home circumstances or time. There were no symptoms history of psychiatric disorders or relevant family history. She did not take medicines and denied use of tobacco or alcohol.

The symptom evolution of the patient presented typical neurophysiological symptoms during the development instead of at the very beginning of the disease. She also reported FBDS (faciobrachial dystonic seizure) episode

(supplementaryfile1). Her MMSE (minimal state examination) was 3/30 (orientation 1, memory 1, language 1). Detailed neurological examination showed a lack of coordination, including normal cranial nerves, predicted IV symmetric strength throughout, active reflexes, incooperated finger-to-nose testing. On physical examinations, she had a normal cardiovascular, respiratory, abdominal, and pulmonary examination during the reported medical history. Cerebral and pituitary MRI (magnetic resonance imaging) (Figure 1 A, B) scans were normal. EEG (electroencephalogram) showed accidental sharp and slow wave complex in bifrontal and biparietal leads (Figure 1 E) with diffuse theta and delta wave background during FBDS, sLORETA (Standardized low-resolution brain electromagnetic tomography)spike source analysis by ASA 4.9 software showed the sharp and slow wave complex were sourced in frontal lobe (Figure 1 C, D). A cell based assay showed serum VGKC (voltage-gated potassium channels) complex proteins (EUROIMMUN, Germany) serum LGI1-Ab to be positive (1:100) while the CSF LGI1-Ab was negative; other autoimmune encephalitis antibodies including AMPA1 (glutamate receptor, ionotropic, alpha1), AMPA2 (glutamate receptor, ionotropic, alpha2), Casp2, cerebellum-1, GABAR (gamma aminobutyric acid receptors),NMDAR (N-methyl-D-aspartate receptors) in serum and CSF were all negative, which established the diagnosis of anti-LGI1 encephalities. CSF (Cerebral spinal fluid) tests for protein, cells, glucose, chloride and culture were normal. Serum sodium ranged between 118-148mmol/L during the reported medical history. FEurate was increased after correction of her hyponatremia (Table 1), which is in consistent with RSW and not SIADH[5] (Table 2). The increased aldosterone during the period of hyponatremia was in consistent with RSW; the cortisol, FT4 and TSH were normal, which excluded hypothyroidism and Addison's disease. Autoimmune, infectious, endocrinologic, neoplastic and paraneoplastic screenings were unremarkable. The IHC staining of LGI1 protein expression in kidney and renal cell carcinoma to explore the underlying LGI1 related RSW mechanism (Figure 2). Note expression of LGI1 in normal renal tubule (C, D) and absence in renal carcinoma tissue (E, F). There was reduced expression of LGI1 in the patient when circulating LGI1 antibody was present as compared to absence of LGI1 antibody (C, D). There was higher expression of LGI1 in proximal as compared to distal convoluted tubules (C, D).

The treatments were given and modulated according the evolution of diagnosis and evaluation of the main symptoms (Figure 1). When the LGI1 antibody encephalitis diagnosis were established, treatment with IVMP (intravenous methylprednisolone) 1.0/day for 5 days, 0.5/day for 3 days, 0.125/day for 5 days, followed with IVIG (intravenous immunoglobulin) at a dose of 0.4 g/kg/day for 5 days 0.4 g/kg/day for 5 days and continued oral prednisolone 40 mg/day treatment for a month declined to 8mg/day maintained. VPA (valproic acid sodium)0.5 oral bid combined OXC (oxcarbazepine) 0.3 oral bid were administered to prevent epilepsy recurrence. The patient's neurological dysfunction responded well to immunoglobulin with diminution of facial muscle jerk as FBDS and improved MMSE scores during the IVIG and consisted afterwards, which increased to 15/30(orientation 6, memory and recall ability 2, attention and calculation 2, language 3, executive function 2, visual spatial 0) after IVIG therapy, and jump to 22/30(orientation 8, memory and recall ability 4, attention and calculation 4, language 3, executive function 3, visual spatial 0) at 6-month follow up, 27/30(orientation 10, memory and recall ability 6, attention and calculation 4, language 3, executive function 3, visual spatial 1) at 2-year follow up. For hyponatremia, which firstly observed after renal carcinoma resection, the patient received saline supplementary as 10% sodium chloride solution intravenous1.5% sodium chloride 250ml qd-bid plus 20ml oral bid-qid according to the serum sodium level. For both the treatment response of saline supplementary and lab investigations of elevated FEurate indicated the diagnosis of RSW instead of SIADH. No hyponatremia and other complaints were observed at the 6 month and 2 year follow up.

Discussion And Conclusion

The diagnosis of encephalitis was not initially entertained when the patient presented with fatigue and found to have hyponatremia, but the development of more obvious symptoms such as repeated falls and FBDS episode were highly suggestive of a paraneoplastic condition associated with LGI1 encephalitis. There has been a growing interest and understanding of paraneoplastic encephalitis and autoimmune encephalitis. Since the 1980s, there has been investigations which identified 2 major groups of antigens that categorize paraneoplastic autoimmune encephalitis, the classic onco-neuronal antigens that include Yo, Hu, Ri, Tr, CRMPs (Amphiphysin, collapsin response mediator proteins), Recoverin, Ma; autoimmune synaptic antigens including NMDAR, AMPAR, LGI1, Casp2, GABAR and unknown antigens[6]. Paraneoplastic autoimmune encephalitis has been reported in patients with lung small cell carcinoma, adenocarcinoma of breast, ovarian teratom, lung cancer etc[3]. We present a rare case of renal carcinoma related paraneoplastic encephalitis, which has been reported previously in 3 cases over the last 2 decades, the diagnosis being hampered in most by a lack of specific antigens[7-9]. For example, a hallucinating 66 year old with renal cell carcinoma had a diagnosis of limbic encephalitis made on the basis of tests for intracellular autoimmune encephalitis that included Hu, Yo antibody but failed to identify antibodies in serum or CSF extracellular antibodies including NMDAR, AMPAR, LGI1, Casp2, GABAR[7], which would be possible autoimmune encephalitis antigens. On the other hand, anti-LGI1 antibody was first reported in 2010 as an extracellular autoimmune factor which targeted the nervous system and was thought to play a role in paraneoplastic autoimmune encephalitis[10]. In time LGI1 paraneoplastic encephalitis or anti-LGI1 encephalitis have been reported in lung cancer[11] and thymoma[12]. The diagnosis of this rare condition can thus be challenging for primary care physicians and it is our hope that this report will raise the awareness and highlight the characteristic presentation of patients with paraneoplastic anti LGI1 encephalitis. In spite of the lack of a clear line to distinguish the paraneoplastic encephalitis and anti-LGI1 encephalitis, the main characteristic presentations of anti-LGI1 encephalitis could be summarized as follows: 1. Serum or CSF LGI1 antibody; 2. Neuropsychic-disorder as memory decline, disorientation or hallucination; 3. Tonic seizure like FBDS; 4. Hyponatremia related symptoms.

The LGI1 gene was discovered in 1980s, which encodes a protein LRR (leucine-rich repeats) with conserved flanking sequences. In the LRR domain, LGI1 shares the highest homology with many transmembrane and extracellular proteins, and these proteins act as receptors and adhesion proteins[13]. LGI1 is primarily expressed in neural tissues, particularly in the brain; it is reduced in low-grade brain tumors and is significantly reduced or eliminated in malignant gliomas[14, 15]. LGI1 was secreted to modulate ADAM22 (a disintegrin and metalloproteinase domain-containing protein 22) or ADAM23 as a secretion protein[1]. LGI1 microrearrangements were observed in a collection of ADLTE (autosomal dominant lateral temporal epilepsy) families and sporadic LTE (lateral temporal epilepsy) patients and investigated novel ADLTE and LTE patients[16]. Anti-LGI1 limbic encephalitis were distinguished from VGKC antibody group encephalitis (anti-LGI1, Caspr2 or VGKC positive groups), and often with hyponatremia, and about half of which have typical FBDS[17-19]. In this report, the patient showed no obvious abnormalities in MRI scans. Which lacks the characteristic imaging presentations in hippocampus[20], striatum[21] and mesial temporal lobes[22]. However, EEG based studies showed hippocampal functional dynamics changes beyond structural damage[19, 23]. In this report, the sLORETA based source analysis showed frontal lobe sourced epileptic foci (Figure 1 C, D), which could shed light on the positioning diagnosis. There is no congruous treatment strategy for autoimmune encephalitis, the accepted therapies are immuno-therapies as steroids and sequenced immunoglobulins[24]. Recently, a strong

influence of a specific HLA (human leukocyte antigen) haplotype has been shown in anti-LGI1 encephalitis in Koreans[25]. In our report, the patient presented with typical features of anti-LGI1 limbic encephalitis, including cognitive defects, FBDS, hyponatremia, and had a good response to steroids and IVIG instead of antiepileptic therapy[26, 27].

Hyponatremia, another characteristic symptom of LGI1 encephalitis patients, defined as serum sodium < 135 mmol/L, is the most common electrolyte abnormality. There is increasing awareness that most or all patients with hyponatremia are symptomatic. The presentations of hyponatremia could be confusion, weakness, in coordination with increased falls and fractures, increasing osteoporosis, irritability, seizures and even death[28]. The recommendation to treat virtually all hyponatremic patients creates a therapeutic dilemma, because untreated patients may suffer the consequences of falls and fractures whereas too rapid correction of > 6 mmol/L/24hrs can lead to osmotic demyelination[29]. It is presently in a state of confusion because the outmoded volume approach has failed to bring clarity to establishing proper diagnosis and thus treatment of this syndrome with multiple etiologies and diverse therapeutic goals. Foremost among this confusion is to differentiate the SIADH for CRSW or more appropriately RSW because of divergent therapeutic goals, to water-restrict a water-loaded patient with SIADH and administer salt and water to a dehydrated patient with RSW. Differentiating SIADH from RSW has been difficult because of the perception that RSW is a rare condition and even more so because of identical clinical parameters that include hyponatremia, hypouricemia, concentrated urine with urine sodium > 30 mmol/L, increased FEurate with normal renal, adrenal and thyroid function[30]. To add further confusion to this diagnostic dilemma, increasing numbers of patients without cerebral disease are being reported with RSW, thus prompting the proposal to change cerebral to renal salt wasting[5]. This change in nomenclature has important clinical implications because RSW would not be considered in the absence of cerebral disease. The inappropriate fluid restriction in RSW for erroneously diagnosed SIADH is therefore, being reported with increasing frequency[30]. There is accumulating evidence to utilize a new algorithm where FEurate is central to our evaluation of hyponatremia. In this algorithm, FEurate is increased to > 11% during hyponatremia in both SIADH and RSW. However, after correction of hyponatremia, FEurate returns to normal in SIADH but remains increased in RSW (Table 1). Our patient with paraneoplastic LGI1 encephalitis had increased FEurate after correction of hyponatremia when serum sodium was 141 mmol/L to meet the criteria for RSW where treatment with saline is most appropriate[30].

The etiology of RSW is most likely due to the presence of a circulating natriuretic peptide that is somehow up-regulated in diverse clinical conditions and is not confined to those with cerebral disease. The natriuretic factor has its major effect in the proximal tubule where uric acid is exclusively transported[31]. When sera from patients with neurosurgical diseases of various etiologies with increased FEurate were injected into rats, FENa and FELithium increased significantly over control values[32]. The nearly 30% increase in FELithium supported our contention that the natriuretic factor has its major effect in the proximal tubule as lithium is predominantly if not exclusively transported passively in the proximal tubule[33]. In this patient, we traced the LGI1 origin in renal tissues for the clues of this phenomena. It is in accordance with previously reported mice LGI1 expressions in renal tubule in mice[34]. It would be interesting to speculate that LGI1 may play a role in the development of the urology carcinoma, as it has been shown for the development of prostate cancer[35]. According to IHC staining studies of the kidney (Figure 2), LGI1 appears to exist more abundantly in the proximal tubule as compared to the distal tubule. The intensity of the staining is reduced when there are circulating antibodies in serum as compared to the absence of circulating antibodies to LGI1. It is interesting that there was absence of staining in

renal carcinoma cells with or without the presence of circulating antibodies. These data indicate that circulating antibodies in sera might be binding to extracellular LGI1 predominantly in the proximal tubule where the major defect in solute transport exists in RSW. However, LGI1 is a potassium channel receptor modulator, its influence on sodium might be intermediated. This could thus lead to generation of putative cytokines that may affect solute transport and induce RSW.

Anti-LGI1 encephalitis with FBDS should be assessed not only structural but also functional measures as EEG based analysis. The sLORETA analysis could provide insight of the Anti-LGI1 encephalitis. Also, LGI1 encephalitis is a multisystem disorder that includes the renal tubule which is manifested as a renal salt wasting syndrome due to a circulating natriuretic peptide and must be differentiated from SIADH because of diametrically opposed therapeutic goals. Anti-LGI1 encephalitis should be a syndrome that is not only confined to patients with encephalitis. However, this case report didn't obtain FEurate before hyponatremia correction, the etiology of hyponatremia as RSW could be evaluated in a large sample of anti-LGI1 encephalitis with or without renal carcinoma, thus lead to the conclusion besides rare circumstances.

List Of Abbreviations

LGI1 leucine-rich anti-glioma 1 protein; FBDS faciobrachial dystonic seizure; RSW renal Salt Wasting; CRSW cerebral/renal salt wasting; FEurate fractional excretion of uric acid; SIADH syndrome of inappropriate secretion of antidiuretic hormone; IHC Immunohistochemistry; MMSE minimal mental state examination; CSF cerebral spinal fluid; MRI magnetic resonance imaging; VGKC voltage-gated potassium channels; AMPA1 glutamate receptor, ionotropic, alpha 1; AMPA2 glutamate receptor, ionotropic, alpha 2; GABAR gamma aminobutyric acid receptors; NMDAR N-methyl-D-aspartate receptors; IVMP intravenous methylprednisolone; IVIG intravenous immunoglobulin; VPA valproic acid sodium; OXC oxcarbazepine; CRMPs amphiphysin, collapsin response mediator proteins; LRR leucine-rich repeats; ADAM22 a disintegrin and metalloproteinase domain-containing protein 22; ADLTE autosomal dominant lateral temporal epilepsy; LTE lateral temporal epilepsy; HLA human leukocyte antigen; SAH subarachnoid hemorrhage.

Declarations

Ethics approval and consent to participate

Written Informed consent and ethical approval were obtained from each subject in accordance with the Helsinki Declaration; the study was approved by the ethical committee of Hainan general hospital.

Consent for publication

Written Informed consent to participate and publication including clinical data, images and videos were obtained from the patient at 6-month follow up, when she had no orientation defections and estimated by 2 attending physicians in neurology department and her family to for the acceptable capacity to make decisions.

Availability of data and material

All data generated or analysed during this study are included in this published article [and its supplementary information files]. The raw datasets used and/or analysed during the current study are also available from the corresponding author on reasonable request.

Competing interests

All of the authors declare no conflict of competing interests.

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Authors' contributions

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. Dr. YL M.D.& P.H.D. -acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. ZCL M.D.-study concept and design, analysis and interpretation of data analysis and interpretation of data analysis and interpretation of data. Pro. JM. -conceptual guidance, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. TL M.D.& P.H.D.-study concept and design, analysis and interpretation of data. analysis and interpretation of data analysis and interpretation of data. Dr. YLH M.D.- analysis and interpretation. Dr. XLX M.D.& M.S-acquisition of data. Pro. GQW M.D.- analysis and interpretation. Dr. QQ M.D.& P.H.D. -study concept, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. SXH M.D.& P.H.D. -study concept, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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Tables

Table 1. Summary of the patient's laboratory findings of hyponatremia correction.

Na	K	PosmmOsm/KgH2O		UA	Creat	Renin	Aldo	All	Cortisol
mmol/L	mmol/L			μmol/L	μmol/L	ng/ml/Hr	pg/ml	pg/ml	nmol/L
141.0	3.86	308		224	83	0.15	129.18	39.36	404
FRT3	FRT4	TSH	Na(Urine)	K(Urine)	Uosm	UA		Creat	FEurate
pmol/L	pmol/L	mIU/L	mmol/24hrs	mmol/24hrs	mOsm/KgH2O	μmol/24hrs		μmol/24hrs	%
4.09	9.82	3.980	28.80	25.22	687	3655		5296	26.93

Posm (plasma osmolality); Uosm (Urine osmolality); All, (angiotensin II); Aldo (aldosterone); creat (creatinine); UA (uric acid); FRT4 (free T4); FRT3 (free T3); TSH (thyroid stimulating hormone); FEurate (fractional excretion of uric acid, FEurate=(serum creatine X urine UA(24hrs))/(serum UA X urine creatin(24hrs))X100%).

Table 2 Differentiation of SIADH from RSW

	RSW	SIADH
ECV	↓	N-↑
UNa	N-↑	N-↑
Renin	↑	±↓
Aldosterone	↑	±↓
Serum urate	↓-↓	↓-N
FEurate	↑-↑	↑-N

ECV, extracellular volume; RSW, renal salt wasting; SIADH, secretion of antidiuretic hormone; UNa, urinary sodium concentration. Table comparing laboratory expectations for RSW and SIADH. UNa can be normal or often $\geq 20\text{mmol/l}$; serum urate and FEurate are increased during hyponatremia in both RSW and SIADH but differ when serum is normal. Serum urate and FEurate remain abnormal in RSW and normalize in SIADH when serum sodium is normal.

Figures

Figure 1

MRI, EEG and spike sLORETA analysis presentations of the patient. The patient presented normal MRI (A, B); slow and accidental sharp and slow wave complex in bifrontal and biparietal leads with diffuse theta and delta wave background during FBDS (E), sLORETA (Standardized low-resolution brain electromagnetic tomography) spike source analysis by ASA 4.9 software showed the sharp and slow wave complex were sourced in frontal lobe (C, D).

Figure 2

Expression of LGI1 by patient's carcinoma. Tumor junction tissue sections of the patient's renal clear cell carcinoma from a patient with serum LGI1 antibodies (A, C, E), another patient with only renal clear cell carcinoma without serum LGI1 antibodies (B, D,F). A commercial antibody against LGI1 (rabbit polyclonal anti-LGI1, abcam, ab137045, diluted 1:50) was used for IHC. Note the expression of LGI1 in normal renal tubule (C,D) and absent in carcinoma tissue (E,F), and the reduced expression pattern in the patient with LGI1 serum antibody (C,D), and higher expression in proximal than distal convoluted tubules (C,D). (The bar presented 20µm, 10µm, 10µm for A,C,E,respectively).

Supplementary Files

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