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CASE REPORT

Primary adrenal insufficiency developed 22 years after the diagnosis of light and heavy chain deposition disease: a case report

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Abstract

Monoclonal immunoglobulin deposition diseases (MIDDs), including light and heavy chain deposition disease (LHCDD), are rare and heterogeneous disorders associated with underlying B-cell clonal disorders. Adrenal involvement is a potential extrarenal manifestation of MIDDs; however, limited data are available regarding its prevalence and clinical presentation. Herein, the present report describes, for the first time, a case of primary adrenal insufficiency that developed twenty-two years after a diagnosis of LHCDD had been made. A 69 year-old woman with a 10 year history of hemodialysis suddenly became bedridden after falling down stairs in the absence of focal neurological deficits. Subsequently, she experienced appetite loss, nausea, vomiting, a fever of unknown origin, and unexplained hypotension. Several months later, primary adrenal insufficiency and normal pressure hydrocephalus were diagnosed and successfully managed. The long-term clinical prognosis of MIDDs has not been fully elucidated despite recent advances in the management of the disorders. This report may contribute to improving our understanding of the disease course.

Keywords Hemodialysis · Light and heavy chain deposition disease · Monoclonal immunoglobulin deposition disease · Normal pressure hydrocephalus · Primary adrenal insufficiency

Abbreviations

AI	Adrenal insufficiency
CST	Corticotropin stimulation test
ESRD	End-stage renal disease
FLC	Free light chains
HDS-R	The revised Hasegawa's dementia scale
LHCDD	Light and heavy chain deposition disease
LP	Lumboperitoneal
MIDDs	Monoclonal immunoglobulin deposition diseases
NPH	Normal pressure hydrocephalus
PTH	Parathyroid hormone
PVCs	Premature ventricular contractions

Introduction

Non-amyloid monoclonal immunoglobulin deposition diseases (MIDDs) are rare and heterogeneous disorders characterized by the production of monoclonal light and/or heavy chains, which are deposited in tissues and cause organ dysfunction [1]. Three subtypes of MIDDs have been reported: light-chain deposition disease, light- and heavy-chain deposition disease (LHCDD), and heavy-chain deposition disease. The kidneys are the most commonly affected organs. The effect often manifests as a nephrotic syndrome and a progressive decline in renal function. Other organs may be affected, such as the heart, liver, peripheral nerves, blood vessels, and adrenal glands [2, 3]. MIDDs always occur in association with underlying B-cell clonal disorders, comprising mainly monoclonal gammopathy of renal significance (approximately two-thirds), symptomatic multiple myeloma (approximately one-third), and rarely, non-Hodgkin B-cell lymphoma [1, 4]. Current management strategy for MIDDs involves bortezomib-based chemotherapy and monitoring of hematological responses by serial measurement of serum free light chains (FLC). Renal and overall outcomes significantly improved after the introduction of bortezomib and FLC measurements compared with high dose melphalan and

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autologous stem cell transplantation, which were previously mainstay of treatment despite the increased morbidity and mortality in patients with impaired renal function [5].

The present report describes a patient with end-stage renal disease (ESRD) attributed to LHCDD, in whom primary adrenal insufficiency (AI) complicated with normal pressure hydrocephalus (NPH) developed 22 years after the diagnosis of LHCDD was made.

Case report

A 69 year-old woman with a 10 year history of hemodialysis was transferred to our long-term care hospital after 6 months in a rehabilitation hospital. She had been a hairdresser in her own beauty shop for the last 25 years and had regularly attended a hemodialysis facility by bicycle for the last 10 years. In the last year, falls from bicycle occurred once every 2 or 3 months, while she could still work as ever. Albumin-corrected serum calcium, phosphate, and parathyroid hormone (PTH) levels were within guideline-recommended target ranges (9.1–9.4 mg/dL, 3.9–5.4 mg/dL, and 80–160 pg/mL, respectively) with the administration of 5 mg evocalcet per day and 2.5 µg maxacalcitol per week [6]. Six months prior, she fell down stairs and bruised her head. She was admitted to an acute hospital, as she was unable to get up herself. Head computed tomography (CT) showed a thin acute subdural hematoma in the left frontoparietal lobe and a subcutaneous hematoma in the right occipital region (Fig. 1). Focal neurological deficits, such as hemiparesis, dysarthria, and ataxia, were not observed. She had a decreased appetite. Two days later, the subdural hematoma had been partially absorbed. She was discharged from the hospital without any improvement of the condition of being unable to perform activities of daily living with a decreased appetite. The following day, she was admitted to another rehabilitation hospital. Cognitive function was assessed by the Revised Hasegawa's dementia scale (HDS-R) (26 points) (the cut-off point for cognitive impairment was 20 points or less). Activities of daily living gradually improved until ambulation exercises were performed within the next 2 months. Follow-up head CT showed the complete disappearance of the subdural hematoma. However, nausea, vomiting, and fever of unknown origin suddenly developed and persisted after a certain dialysis session. The effect resulted in impairment in activities of daily living again, further deteriorated anorexia, and a decline in the HDS-R score (20 points) over the next 4 months. Hemodialysis frequency was reduced from thrice to twice weekly sessions due to the absence of interdialytic weight gain. The dry weight was reduced by 12 kg over the 6 months following admission. Mild hypercalcemia (albumin-corrected serum calcium 11–12 mg/dL) also developed despite the cessation of maxacalcitol. The patient was eventually transferred to our hospital. Her medical history was notable for nephrotic syndrome associated with LHCDD, diagnosed by a kidney biopsy 22 years ago in the absence of any evidence of multiple myeloma. The detailed biopsy findings were unavailable. Steroid treatment failed to prevent the progression of the condition to ESRD. Hemodialysis was initiated 12 years after the diagnosis of LHCDD. The medical history also revealed endovascular coil embolization for a symptomatic unruptured cerebral aneurysm of the right internal carotid artery 6 years ago. She had no relevant history of

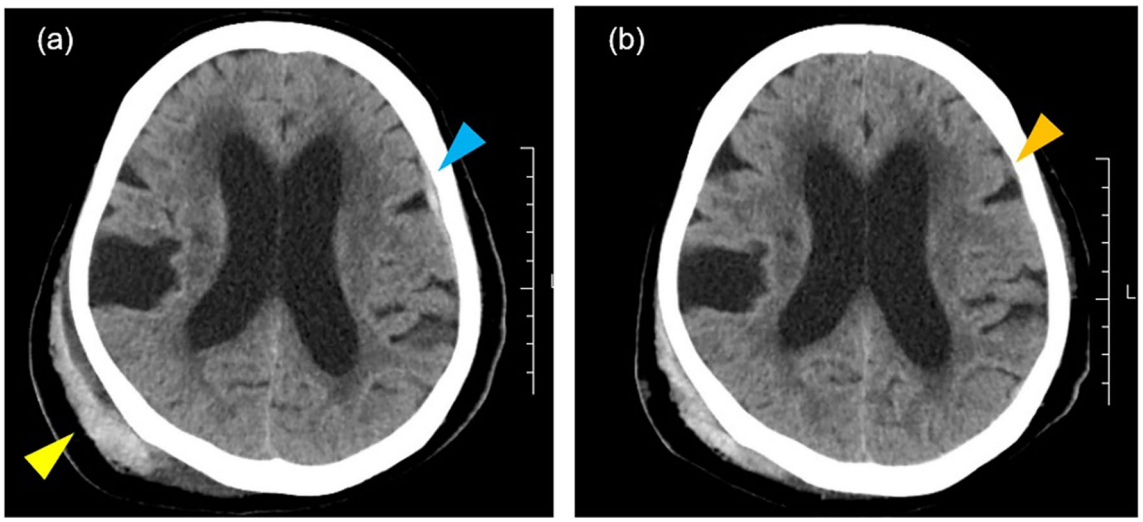

Fig. 1 **a** A brain computed tomography (CT) scan following a fall down stairs shows a thin subdural hematoma (blue arrowhead) in the left frontoparietal lobe and a subcutaneous hematoma (yellow arrowhead) in the right occipital region. **b** A repeat CT, 2 days after the fall, demonstrates the already partially absorbed subdural hematoma (orange arrowhead)

arrhythmia. Physical examination was significant for marked pitting edema of her limbs bilaterally. Her blood pressure was 129/83 mmHg, her pulse was 78 beats/min and regular, and her body temperature was 37.3 °C. Chest radiography revealed an enlarged heart (cardiothoracic ratio, 0.60) and right-sided pleural effusion.

Reduction in dry weight was difficult due to the low systolic blood pressure of approximately 100 mmHg during dialysis sessions despite normal left ventricular systolic function showed by echocardiography and signs of fluid overload. Laboratory tests revealed anemia (hemoglobin 7.4 g/dL), hypoproteinemia (serum total protein 4.7 g/dL), hypoalbuminemia (serum albumin 2.8 g/dL), mild hypercalcemia (albumin-corrected serum calcium 11.6 mg/dL), hypophosphatemia (2.6 mg/dL), a PTH level within the target range (74 pg/mL), a low 1,25-dihydroxyvitamin D3 level (6 pg/mL) (normal range 20–60 pg/mL), and a C-reactive protein level below the cut-off value (0.3 mg/dL) (Table 1). Serum FLC analysis showed κ FLC 116.9 mg/L (normal range 3.3–19.4 mg/L), λ FLC 217.9 mg/dL (normal range 5.7–26.3 mg/L), and FLC ratio of 0.54 (reference range applied to patients with eGFR ≤ 55 mL/min/1.73 m^2 0.82–3.6), which were compatible with the diagnosis of LHCDD [1, 4, 7]. Neither evidence of monoclonal gammopathy on serum protein electrophoresis nor osteolytic bone lesions on skeletal survey were detected. The unexplained hypotension and the above-mentioned clinical course in the previous hospitals raised a suspicion of AI. A

Table 1 Laboratory results

Parameter	Value
Leukocyte count (/μL)	3130
Eosinophil count (/μL)	128
Hemoglobin (g/dL)	7.4
Platelet count ($\times 10^4$/μL)	13.3
Urea nitrogen (mg/dL)	30.8
Creatinine (mg/dL)	6.74
Glucose (mg/dL)	89
Serum total protein (g/dL)	4.7
Albumin (g/dL)	2.8
Aspartate transaminase (U/L)	11
Alanine transaminase (U/L)	3
Lactate dehydrogenase (U/L)	136
Sodium (mEq/L)	140
Potassium (mEq/L)	3.6
Chloride (mEq/L)	107
Corrected serum calcium (mg/dL)	11.6
Phosphate (mg/dL)	2.6
C-reactive protein (mg/dL)	0.1
Parathyroid hormone (pg/mL)	74
1,25-dihydroxyvitamin D3 (pg/mL)	6
Beta 2-microglobulin (mg/L)	31.0
T-SPOT. TB	Negative
Antinuclear antibody indirect immunofluorescence assay	Negative
Thyroid-stimulating hormone (μIU/mL)	2.7
Free thyroxine (ng/dL)	1.0
Adrenocorticotropic hormone (pg/mL)	15.7
Serum cortisol (μg/dL)	Baseline: 10.7 60 min after intravenous administration of 250 μg of corticotropin: 19.5
Serum aldosterone (pg/mL)	Less than the detection limit
Plasma renin activity level (supine)(ng/mL/h)	2.6
Serum protein electrophoresis	No monoclonal spike
Free light chains κ (mg/L)	116.9
Free light chains λ (mg/dL)	217.9
The ratio of κ and λ free light chains	0.54

250 µg corticotropin stimulation test (CST) during morning fasting on a non-dialysis day showed a stimulated cortisol level slightly above the cut-off level (18 µg/dL) with a low incremental response (baseline: 10.7 µg/dL; after 60 min: 19.5 µg/dL). Adrenocorticotropic hormone level (15.7 pg/mL) was within the normal range (7.2–63.3 pg/mL). Serum aldosterone level was less than the detection limit, while supine plasma renin activity level was slightly elevated (2.6 ng/mL/h) (normal range 0.2–2.3 ng/mL/h). These findings were interpreted as primary AI in its early stages, with certain underlying comorbidities leading to an increased corticosteroid requirement. Abdominal CT scan showed bilateral adrenal atrophy. The results of a T-SPOT. TB and blood cultures were negative. 21-hydroxylase autoantibodies were not measured, as the Japanese health insurance system does not cover them. In this case, LHCDD was a potential cause of primary AI. Another possible cause was dialysis-related amyloidosis despite the lack of characteristic manifestations such as carpal tunnel syndrome. A beta 2-microglobulin level (31.0 mg/L) was slightly high (the target value was 30 mg/L or less). She refused biopsies, which might lead to a definitive diagnosis. Physiologic corticosteroid replacement (10 mg hydrocortisone in the morning) promptly increased the systolic blood pressure to 150 mmHg, facilitated further fluid removal, lowered the frequency of fever, and improved food intake to 1,000 kcal/day. She transitioned to thrice-weekly hemodialysis. As vomiting after assistive bathing persisted, hydrocortisone was increased as follows: 20 mg/day for non-dialysis days and 25 mg/day for dialysis days, divided into 2 or 3 doses per day (10 mg in the morning, 5 mg before dialysis, and 10 mg in the afternoon). For further investigation, a head CT was performed, which indicated ventriculomegaly (Evans index 0.36), enlarged Sylvian fissures, and a tight high convexity (Fig. 2). The findings and symptoms such as vomiting, cognitive impairment, and loss of mobility were compatible with a diagnosis of NPH [8]. Images of head CT scans in the previous hospitals were obtained. These retrospectively showed similar but milder findings suggestive of early-stage NPH. After confirming the effectiveness of the cerebrospinal fluid tap test, a lumboperitoneal (LP) shunt was placed in the initial acute care hospital. Cognitive function and food intake significantly improved (HDS-R 25 points and 1,400 kcal/day, respectively), with the disappearance of vomiting and febrile

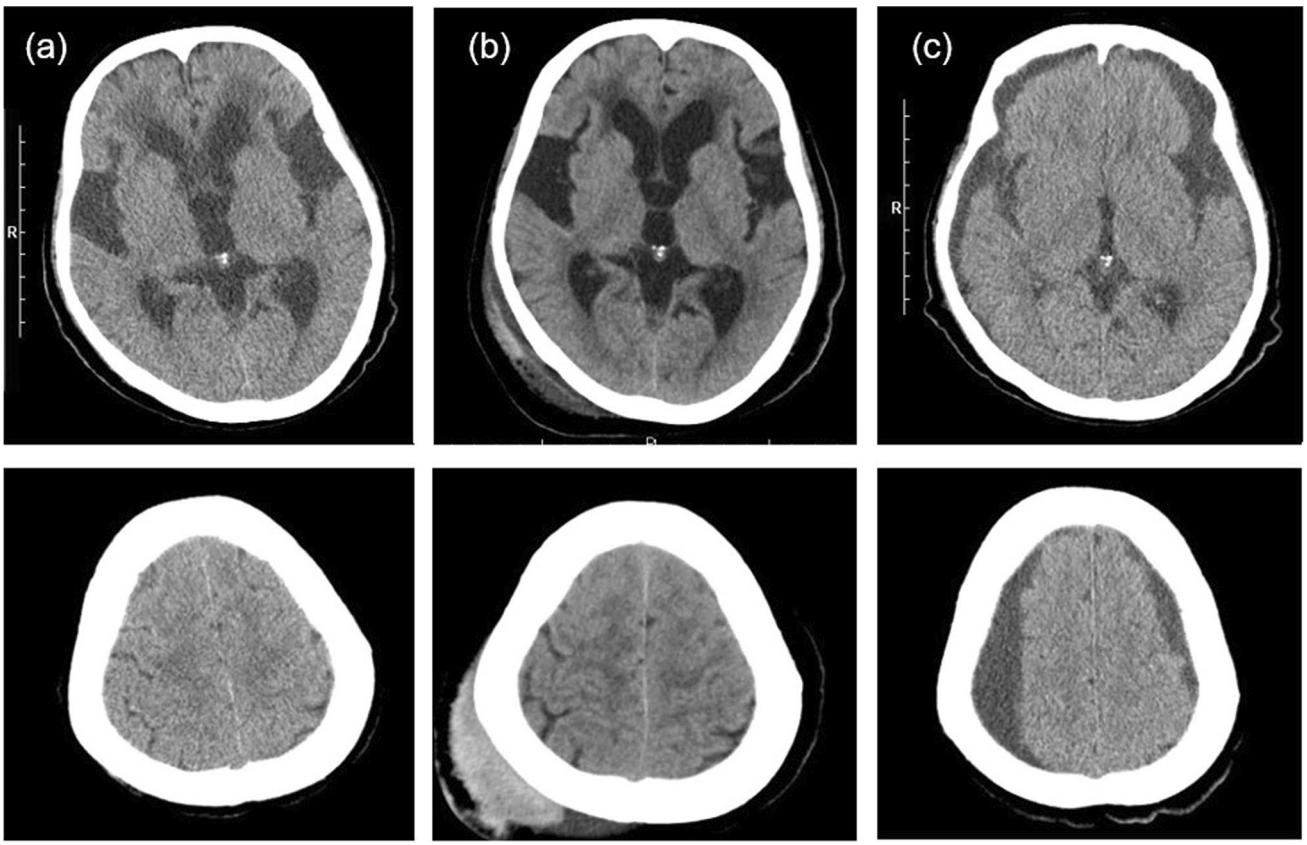

Fig. 2 **a** A brain computed tomography (CT) scan 6 months after falling down stairs shows ventriculomegaly (Evans index 0.36), enlarged Sylvian fissures, and a tight high convexity. **b** Retrospectively, the initial brain CT scan exhibits similar ventriculomegaly (Evans index 0.35) and enlarged Sylvian fissures, while the high-convexity tightness is milder. **c** A brain CT scan 1 month after the lumboperitoneal shunt insertion shows accumulation of cerebrospinal fluid in the subdural space caused by shunt overdrainage

episodes. The mild hypercalcemia remained unchanged. Subsequently, several adjustments of the shunt valve opening pressure were required due to overdrainage or underdrainage. When the shunt valve pressure was incorrectly set, the effect presumably acted as a stressor and led to the recurrence of appetite loss and low-grade fever. Similarly, large movements of the distal end of the catheter were observed on plain radiography in association with appetite loss and low-grade fever in addition to abdominal distension (Fig. 3). This complication resolved spontaneously within a few weeks. She subsequently exhibited frequent premature ventricular contractions (PVCs), which was successfully treated with bisoprolol. Abnormal liver function was not observed. The second 250 μg CST three months after the first evaluation failed to increase serum cortisol (baseline: 6.8 μg/dL; after 1 h: 11.0 μg/dL) and suggested further progressed adrenal hypofunction. Therefore, the dose of hydrocortisone was maintained. The pitting edema gradually disappeared. The reduced mobility remained roughly unchanged presumably due to a long-term bed rest of > 6 months. Except for the minor complications associated with the LP shunt system and PVCs, the patient had an uneventful course for 13 months following the LP shunt insertion. The clinical course is shown in Fig. 4.

Discussion

Adrenal involvement is a potential extrarenal manifestation of MIDDs but limited data are available concerning its prevalence and clinical presentation [2, 3]. Light-chain deposits in the adrenal gland have been reported in some autopsy studies of MIDD patients without an AI diagnosis. One study showed that one in 11 patients with MIDDs had endocrine dysfunction of central origin (AI, hypothyroidism, diabetes insipidus, and hypogonadism) that did not improve after high dose chemotherapy [5]. This is the first report to describe a clinically diagnosed case of primary AI associated with MIDD. Previous studies have shown that MIDD deposits can be found in virtually all tissues and organs frequently in the absence of clinical symptoms [3]. The development of clinical manifestations associated with extrarenal tissular deposits may depend on the extent of deposition and the nature of the precursor protein. The precise etiology of this condition is unknown. Further accumulation of cases is required in the future.

Detecting AI at an early stage is challenging without generally accepted recommendations for diagnostic strategies, especially in patients with underlying comorbidities [9–11]. Yamamoto suggested the clinical utility of stress-related health changes disproportionate to the severity of stress and quick recovery following the resolution of stress as clues for the diagnosis of latent primary AI [9]. In this case, a significant impairment of daily functioning out of proportion to the physical and radiological findings after a fall led to a suspicion of AI. The absence of recovery was attributed to a persistent stressor, i.e., NPH. Previous studies showed that the standard dose (250 μg) CST might miss some cases of latent primary AI due to supra-physiological stimulation [12, 13]. The potential diagnostic test includes a low-dose (1 μg) CST, although it has not been fully validated [9, 14]. Thus, while awaiting

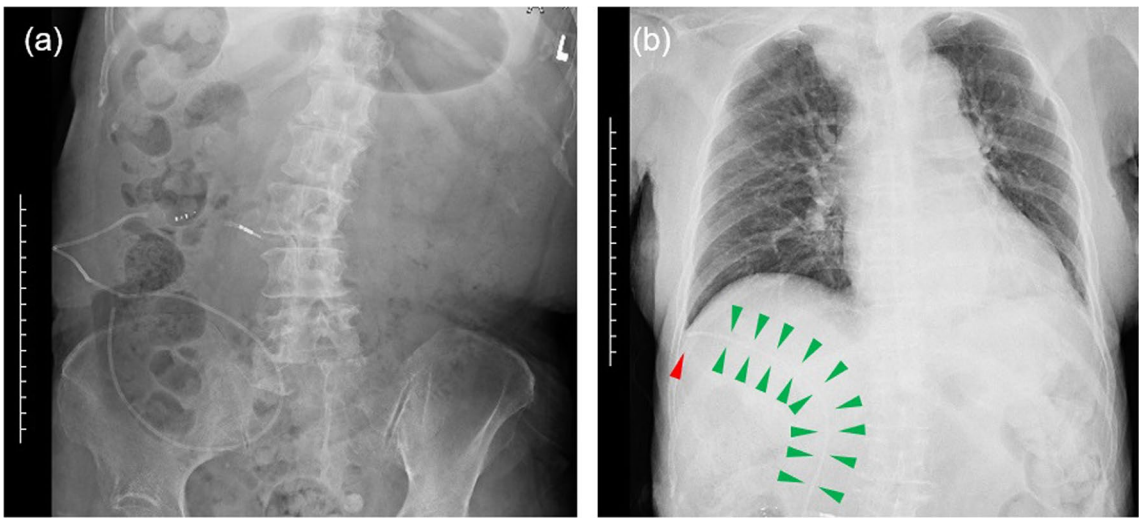

Fig. 3 **a** A plain abdominal radiograph following the lumboperitoneal shunt insertion shows the distal catheter located in the lower right-hand part of the abdominal cavity. **b** A plain chest radiograph shows the distal catheter of the lumboperitoneal shunt located in the upper right-hand part of the abdominal cavity (green arrowheads) and the distal end of the catheter immediately beneath the diaphragm (red arrowhead)

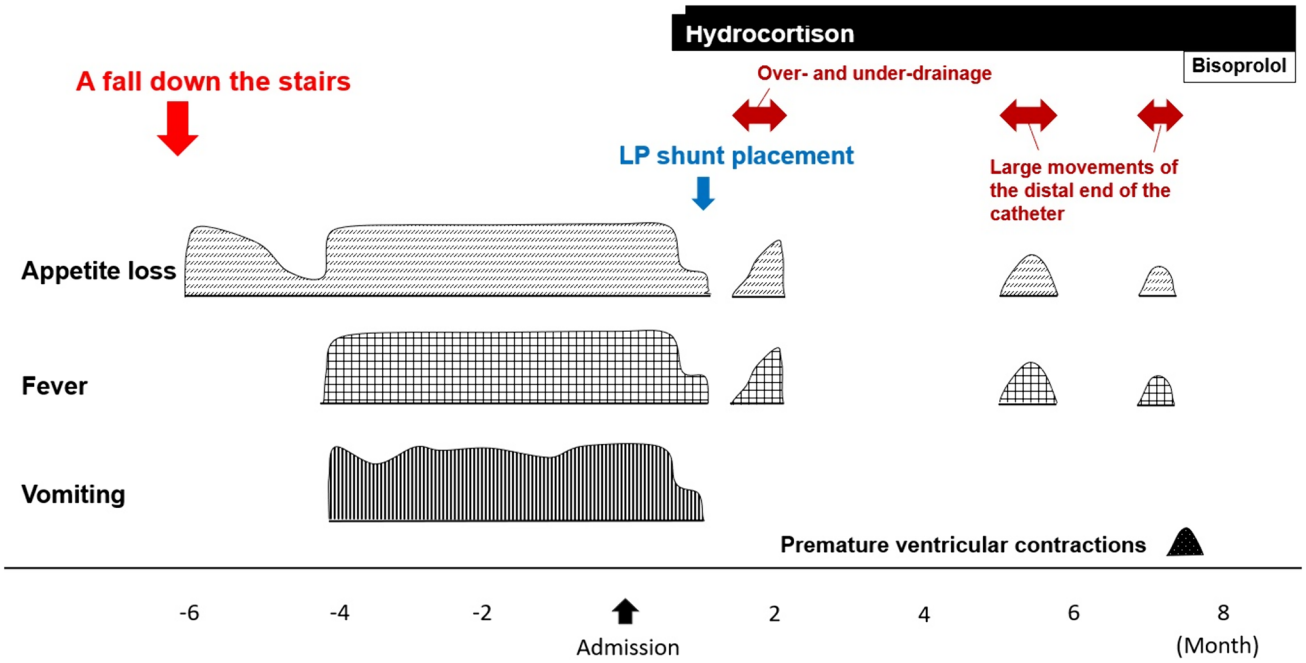

Fig. 4 Time course of treatment with clinical symptoms and complications associated with lumboperitoneal (LP) shunting

more diagnostic factors than cortisol, the clinician might adopt the following pragmatic attitude: in patients with suspected AI, even if serum cortisol concentration after administration of corticotropin is slightly higher than the cut-off level, progressively worsening symptoms may allow evaluation of the effect of hydrocortisone substitution within the range corresponding to physiological cortisol production (15–25 mg or 7.5–15 mg/m^2/day) [15]. When the patient's general condition is not so impaired, repeated testing should be scheduled without administering hydrocortisone.

LP shunting has been associated with several complications, including overdrainage, shunt obstruction, migration, infection, and abdominal complications such as intestinal obstruction, volvulus, and bowel perforation [16–19]. In many cases, programmable shunt valves combined with an anti-siphon device can non-invasively manage over- and under-drainage without surgical revision and reduce the incidence of overdrainage-induced chronic subdural hemorrhage. Bowel movements may enhance intra-abdominal migration and lead to abdominal complications, which can be fatal in some cases [17]. In the case described here, only minor complications were observed. However, the effects in this case with AI were presumably larger than those in subjects without AI.

In summary, primary AI complicated by NPH developed 22 years after the diagnosis of LHCDD was made. The long-term clinical prognosis of MIDDs has not been fully elucidated despite recent advances in the management of these disorders. This report may contribute to improving our understanding of the disease course.

Declarations

Conflict of interest The author has declared that no Conflict of interest exists.

Informed consent Informed consent was obtained from the patient included in the study.

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