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Case Report with Review of Literature

Post-traumatic pituitary stalk transection syndrome (PSTS) expeditiously manifested after a fall from a height combined with acute traumatic spinal cord injury: a rare case report with review of literature

Yohei Ishiki, Atsuko Tamaki, Ken-ichiro Honma, Ken Yonaha, Takamitsu Yabiku, Taiki Teruya, Moriyuki Uehara, Yoshiro Nakayama, Rei Chinen, Tsugumi Uema, Sawako Nakachi, Shiki Okamoto and Hiroaki Masuzaki

Division of Endocrinology, Diabetes and Metabolism, Hematology and Rheumatology, Second Department of Internal Medicine, Graduate School of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan

Abstract. Post-traumatic pituitary stalk transection syndrome (PSTS) is an extremely rare cause of combined pituitary hormone deficiency (CPHD), affecting approximately 9 per 100,000 cases of traumatic brain injury. In contrast, pituitary stalk interruption syndrome (PSIS) is also a rare cause of CPHD. Importantly, these conditions are often confused due to their similar names and resembling findings on magnetic resonance imaging (MRI). PSIS has been thought to be a prenatal developmental event resulting from a couple of genetic aberrations. In typical PSIS, anterior pituitary hormone deficiencies are restricted to growth hormone (GH) and gonadotropin during the pediatric age, gradually and generally progressing to panhypopituitarism in most cases. In contrast, global deficiencies of the anterior pituitary hormones in PSTS are temporally associated with trauma. To the best of our knowledge, no case reports of PSTS combined with acute traumatic spinal cord injury have been reported. A 34-year-old female was transferred to our hospital after jumping from the fourth building floor. She was diagnosed as an acute traumatic spinal cord injury and underwent the operation of elective posterior spinal fusion. On postoperative day 7, the blood tests revealed considerable hyperkalemia, hyponatremia and eosinophilia. Notably, menstruation stopped after falling from a height. Pituitary function tests revealed GH deficiency, hypogonadism, hypothyroidism and hypoadrenocorticism. MRI revealed loss of the pituitary stalk, whilst the hyperintense signal from distal axon of hypothalamus was still identified. Based on these findings, she was diagnosed as PSTS. Our case highlights endocrinological landscape of transection of the pituitary stalk by acute trauma.

Key words: Post-traumatic pituitary stalk transection syndrome (PSTS), Pituitary stalk interruption syndrome (PSIS), Acute traumatic spinal cord injury, Secondary adrenal insufficiency, Combined pituitary hormone deficiency

Introduction

Post-traumatic pituitary stalk transection syndrome (PSTS) is a rare cause of combined pituitary hormone deficiency (CPHD). It has been reported that occurrence of traumatic brain injury is approximately 235 per 100,000 persons per year, with PSTS accounting for approximately 4% of all cases [1, 2]. PSTS is an acquired consequence of head trauma, leading to regenerative and regressive changes in the hypothalamic-pituitary region, which occasionally mimics closely genetic pituitary stalk interruption syndrome (PSIS) on magnetic resonance imaging (MRI) findings [3].

PSIS was initially reported in 1987, which is accompanied by both an ectopic posterior pituitary gland (EPP) and an interrupted stalk [4]. Incidence of PSIS has recently been increasing due to routine use of MRI as a primary radiological modality in patients with hypopituitarism [5]. A previous report demonstrated that PSIS was found about 7% in approximately 15,000 patients with growth hormone (GH) deficiency [6]. Nowadays, MRI reveals numerous anatomical variations in patients with PSIS, encompassing alterations in the anterior pituitary lobe (*e.g.*, absence, hypoplasia or normal), the

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Correspondence to: Hiroaki Masuzaki, MD, PhD, Division of Endocrinology, Diabetes and Metabolism, Hematology and Rheumatology, Second Department of Internal Medicine, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan.
E-mail: hiroaki@med.u-ryukyu.ac.jp

posterior pituitary lobe (*e.g.*, absence, ectopic along the stalk, ectopic at the hypothalamus base or normal in the sella turcica), and/or the stalk (*e.g.*, interrupted, thin or normal) [7]. Moreover, molecular pathogenesis of PSIS caused by genetic defects is widely recognized [8].

Here, we report an extremely rare case of an adult female in whom PSTS expeditiously manifested after the fall from heights accompanied by the acute traumatic spinal cord injury.

Case Presentation

A 34-year-old female (height 164 cm, body weight 64 kg, Body Mass Index 23.8 kg/m^2) was transferred to our hospital two days after jumping from the fourth floor of a building (approximately 12 meters) due to a quarrel with her partner. She initially experienced post-traumatic stress disorder stemming from sexual abuse by her father and was prescribed psychotropic medications, including Quetiapine at a dosage of 300 mg/day, Trazodone at 50 mg/day, Eszopiclone at 2 mg/day, Flunitrazepam at 2 mg/day, and Lorazepam at 1.5 mg/day. She had no history of breech delivery or the delayed development of secondary sexual characteristics. The patient's last menstrual period occurred 13 days before the day of jumping, and her menstruation had not resumed even after 200 days following the event. Her menstruation stopped for the first time following the fall from the height. Upon admission, she was fully conscious. However, abrasion was observed in the occipital region. She sustained both of lower limb fractures (right talus and fibula fracture as well as left femur fracture) and vertebral fractures at the level of C2, C6, C7, and T2. Preoperatively, all muscle groups were tested using the manual muscle test (MMT) according to the International Standards for Neurological Classification after Spinal Cord Injury (ISNCSCI). She presented with incomplete tetraplegic, exhibiting an MMT of 1 or 2/5 below the C7 myotome level and the loss of anal tone. However, she demonstrated no paresthesia below the T1 dermatomal level. The ISNCSCI examination results were consistent with C7 ASIA Impairment Scale C tetraplegia. MRI revealed a dislocated fracture of the C7 vertebral body with mild posterior displacement of T1 (Fig. 1). Fortunately, no apparent visceral injury was observed throughout the body, including the liver, spleen, kidney, adrenal gland, aorta, bladder, ovary, uterus or vagina. She then underwent the operation of elective posterior spinal fusion (C3–T4) on the fifth day after the trauma. On the postoperative day (POD) 7, a routine blood test revealed considerable hyperkalemia (potassium [K] 6.7 mEq/L) and slight hyponatremia (sodium [Na] 133 mEq/L), whereas blood urea nitrogen (BUN) and creatinine levels were within the normal range. She represented with no symptoms of adrenal insufficiency such as nausea, vomiting, fatigue, or fever. Value of her blood pressure remained stable at around 90/50 mmHg.

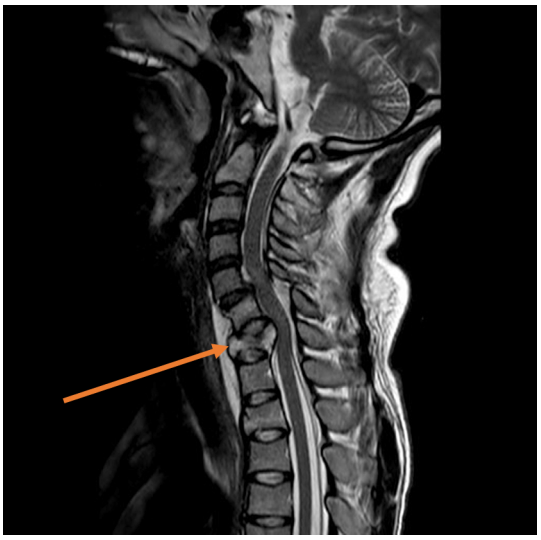

Fig. 1 The fracture of the C7 vertebral body is illustrated in MRI. The T2-weighted sagittal MRI sequence displays a dislocated fracture of the C7 vertebral body with mild posterior displacement of T1 (orange arrow). The 7th cervical spinal cord is compressed by a dislocated fracture at C7.

Laboratory findings of the patient revealed eosinophilia, anemia, elevated serum levels of liver enzymes and prolactin (PRL), hypogonadism, hypothyroidism, secondary adrenal insufficiency and low somatomedin C levels (Table 1). In addition, the level of plasma arginine vasopressin (AVP) was below the measurable range (<0.4 pg/mL), while no clinical manifestations, including dry mouth, polydipsia, and polyuria, were noted. Basal value of hormones in Table 1 was assessed at 31 days after the day of jumping, because she had undergone antimicrobial and infusion therapy. Suspecting combined pituitary hormone deficiency (CPHD), we performed a line of hormone-loading tests to evaluate pituitary function at 31–35 days after the fall. In the corticotropin-releasing hormone (CRH) stimulation test, the response of serum cortisol was apparently blunted (baseline 2.1 μg/dL; peak 12.1 μg/dL), while that of adrenocorticotropic hormone (ACTH) was within the normal range (baseline <1.5 pg/mL; peak 29 pg/mL) (Table 2A). The gonadotropin-releasing hormone stimulation test revealed a delayed response to both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Table 2A). The thyrotropin-releasing hormone test demonstrated that the response of thyroid-stimulating hormone (TSH) was within the normal range, while the response of PRL was slightly blunted (baseline

Table 1 Laboratory Data

Hematology	Value (Reference range)	Biochemistry	Value (Reference range)
WBC, $10^3/\mu L$	4.3 (3.3–8.6)	Calcium, mg/dL	8.8 (8.8–10.1)
Neutro, %	56.0 (40.7–77.0)	CRP, mg/dL	2.27 (0.00–0.14)
Lymph, %	25.5 (16.0–49.5)	TC, mg/dL	152 (142–248)
Eosino, %	10.9 (0.0–8.5)	TG, mg/dL	184 (30–117)
Baso, %	1.6 (0.0–2.5)	HDL-C, mg/dL	24 (48–103)
RBC, $10^6/\mu L$	3.15 (3.86–4.92)	LDL-C, mg/dL	80 (65–163)
Hb, g/dL	9.6 (11.6–14.8)		
Ht, %	29.7 (35.1–44.4)	Endocrine hormones	
PLT, $10^3/\mu L$	498 (158–348)	GH, ng/mL	1.03 (0.00–2.47)
		Somatomedin-C, ng/mL	84 (115–277)
Biochemistry		PRL, ng/mL	132.0 (4.91–29.3)
Total protein, g/dL	5.4 (6.6–8.1)	LH, mIU/mL	<0.3 (1.13–64.3)
Albumin, g/DL	2.8 (4.1–5.1)	FSH, mIU/mL	0.9 (1.79–113.6)
AST, U/L	41 (13–30)	ACTH, pg/mL	5.0 (7.2– 63.3)
ALT, U/L	28 (7–23)	Cortisol, μg/dL	1.76 (6.24–18.0)
Total bilirubin, mg/dL	0.4 (0.4–1.5)	TSH, μU/mL	1.50 (0.3–4.2)
ALP, U/L	77 (38–113)	Free T3, pg/mL	1.2 (2.3–4.0)
LDH, U/L	280 (124–222)	Free T4, ng/dL	0.47 (1.10–1.80)
Creatine kinase, U/L	228 (41–153)	24h UFC, μg/day	Lower limit (4.3–176)
Glucose, mg/dL	80 (73–109)	Urine volume, mL/day	1,900
BUN, mg/dL	12 (8.0–20.0)	P-osm, mOsm/L	274 (275–295)
Creatinine, mg/dL	0.66 (0.46–0.79)	U-osm, mOsm/L	294 (100–1,300)
Na, mEq/L	133 (138–145)	AVP, pg/mL	<0.4 (0.4–3.5)
K, mEq/L	6.7 (3.6–4.8)	PRA, ng/mL/h	3.8 (0.2–2.7)
Cl, mEq/L	99 (101–108)	PAC, pg/mL (CLEIA)	96 (4.0–82.1)

Abbreviations: WBC, White Blood Cells; RBC, Red Blood Cells; Hb, Hemoglobin; Ht, Hematocrit; PLT, Platelet; Neutro, Neutrophil; Lymph, Lymphocytes; Eosino, Eosinophil; Baso, Basophil; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; LDH, Lactate dehydrogenase; Na, Sodium; K, Potassium; Cl, Chloride; TC, Total cholesterol; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; LDL-C, Loc-density lipoprotein cholesterol; GH, Growth hormone; PRL, Prolactin; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; ACTH, Adrenocorticotropic hormone; TSH, Thyroid-stimulation hormone; T3, Triiodothyronine; T4, Tetraiodothyronine; UFC, Urinary free cortisol; P-osm, Plasma osmolality; U-osm, Urine osmolality; AVP, Arginine vasopressin; PRA, Plasma renin activity; PAC, Plasma aldosterone concentration; CLEIA, Chemiluminescent enzyme immunoassay.

132 ng/mL; peak 211 ng/mL) (Table 2A). In the growth hormone-releasing hormone peitide-2 (GHRP-2) test (Table 2B), the GH response was substantially blunted (baseline 1.5 ng/mL; peak 7.7 ng/mL) and the response of serum cortisol was not detected (baseline 0.1 μg/dL; peak 0.9 μg/dL). Moreover, the rapid ACTH test revealed that the response of serum cortisol was also blunted (baseline 1.7 μg/dL; peak 8.3 μg/dL) (Table 2C). At six weeks after the day of jumping, MRI detected a normal size of anterior pituitary lobe, but no visible pituitary stalk was identified (Fig. 2A). Of note, hyperintense signal in the posterior lobe on T1 weighted imaging was disappeared, meanwhile, the hyperintense signal of the distal axon of the hypothalamus was still identified (Fig. 2B). These MRI findings are consistent with the characteristics of PSTS [9, 10].

Based on a series of findings above, she was diagnosed as PSTS accompanied by acute traumatic spinal cord injury. The patient began treatment with hydrocortisone (15 mg/day) and levothyroxine sodium hydrate

(125 μg/day). After adequate hormone replacement, her blood test at four months after the day of jumping revealed as follows: Na 140 mEq/L, K 4.2 mEq/L, TSH <0.10 μU/mL, FT3 2.0 pg/mL, FT4 1.54 ng/dL, ACTH <1.5 pg/mL, cortisol 0.25 μg/dL, PRL 177.0 ng/mL, LH <0.3 mIU/mL, FSH 0.8 mIU/mL, plasma osmolality 294 mOsm/L, urine osmolality 407 mOsm/L, AVP <0.4 pg/mL without polydipsia and polyuria. At six months after the day of jumping, she was transferred to a psychiatric hospital for mental rehabilitation. Fig. 3 provides an overview of the clinical timeline of this case, delineated based on the day of the incident.

Table 2 Hormone-releasing tests

A) CRH/TRH/GnRH test (CRH 100 μg, TRH 200 μg, GnRH 100 μg iv.)					
Time (min)	0	30	60	90	120
ACTH (pg/mL)	<1.5	29.0	21.0	14.3	9.5
Cortisol (μg/dL)	2.1	8.8	11.9	12.1	11.5
TSH (μU/mL)	1.5	14.1	15.0	14.6	12.8
T3 (ng/mL)	0.31		—		0.81
T4 (μg/dL)	3.01		—		4.19
PRL (ng/mL)	132	211	183	157	144
LH (mIU/mL)	<0.3	1.6	1.9	2.0	2.5
FSH (mIU/mL)	0.8	2.7	3.6	4.1	4.8
B) GHRP-2 test (GHRP-2 100 μg iv.)					
Time (min)	0	15	30	45	60
GH (ng/mL)	1.5	7.7	6.6	4.5	2.9
Cortisol (μg/dL)	0.1	0.3	0.9	0.9	0.6
C) ACTH stimulation test (ACTH 250 μg iv.)					
Time (min)	0	30	60		
ACTH (pg/mL)	<1.5		—		
Cortisol (μg/dL)	1.66	6.0	8.3		

Abbreviations: CRH, corticotropin releasing-hormone; TRH, thyrotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; ACTH, Adrenocorticotropic hormone; PRL, Prolactin; TSH, Thyroid-stimulation hormone; T3, Triiodothyronine; T4, Tetraiodothyronine; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; GHRP-2, growth hormone-releasing hormone peitide-2; GH, Growth hormone.

Discussion

PSTS and PSIS are often confused due to their similar names and resembling images in MRI. PSIS is currently thought to represent a prenatal developmental event caused by a couple of genetic aberrations. Mutations in several genes (*e.g.*, *TGIF*, *SHH*, *OTX2*, *SOX3*) have been identified in approximately 5% of the patients studied [11, 12]. Approximately 50% of patients with PSIS have extra-pituitary and midline developmental malformations (*e.g.*, microcephaly, hydrocephalus, type 1 Chiari malformation and cleft lip and/or palate) [13]. In any cases, it should be noted that PSIS never occurs as a consequence of PSTS. Furthermore, distinct hormonal presentations have been observed between PSIS and PSTS. Typical clinical manifestations of PSIS include permanent anterior pituitary hormone deficiencies particularly GH and gonadotropin during the pediatric age, which appear gradually but steadily progress to panhypopituitarism in adulthood. However, very few patients have arginine vasopressin deficiency (AVP-D) compared to other hormonal deficiencies, partly because the anterior and posterior lobes have different embryonic origins [7].

On the other hand, hormonal manifestations of PSTS are temporally related to head trauma, which causes transection of the pituitary stalk [3]. In our case, the patient's menstruation stopped just after the acute traumatic spinal cord injury caused by a fall from a height. Moreover, she

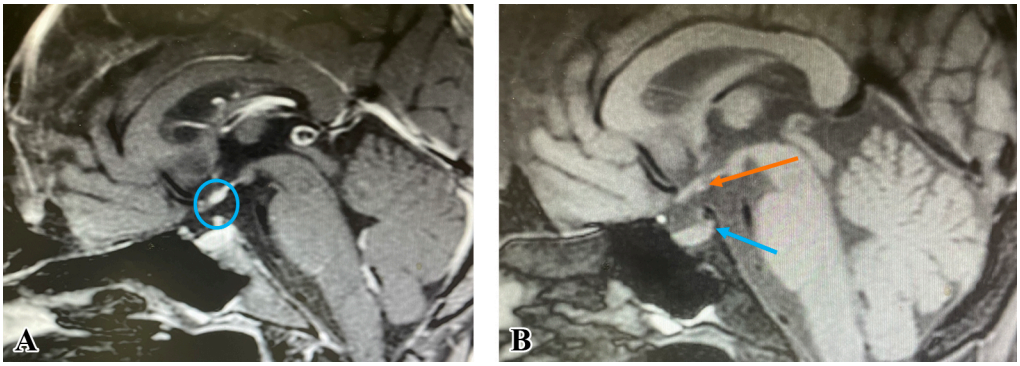

Fig. 2 The findings of post-traumatic pituitary stalk transection syndrome in MRI.
(A) T1-weighted sagittal images after the intravenous injection of gadopentetate dimeglumine MRI sequence demonstrating the loss of the pituitary stalk (blue circled).
(B) The T1-weighted sagittal MRI sequence displays a lack of the hyperintense signal in the posterior lobe (blue arrow) and the hyperintense signal of the distal axon of the hypothalamus (orange arrow).

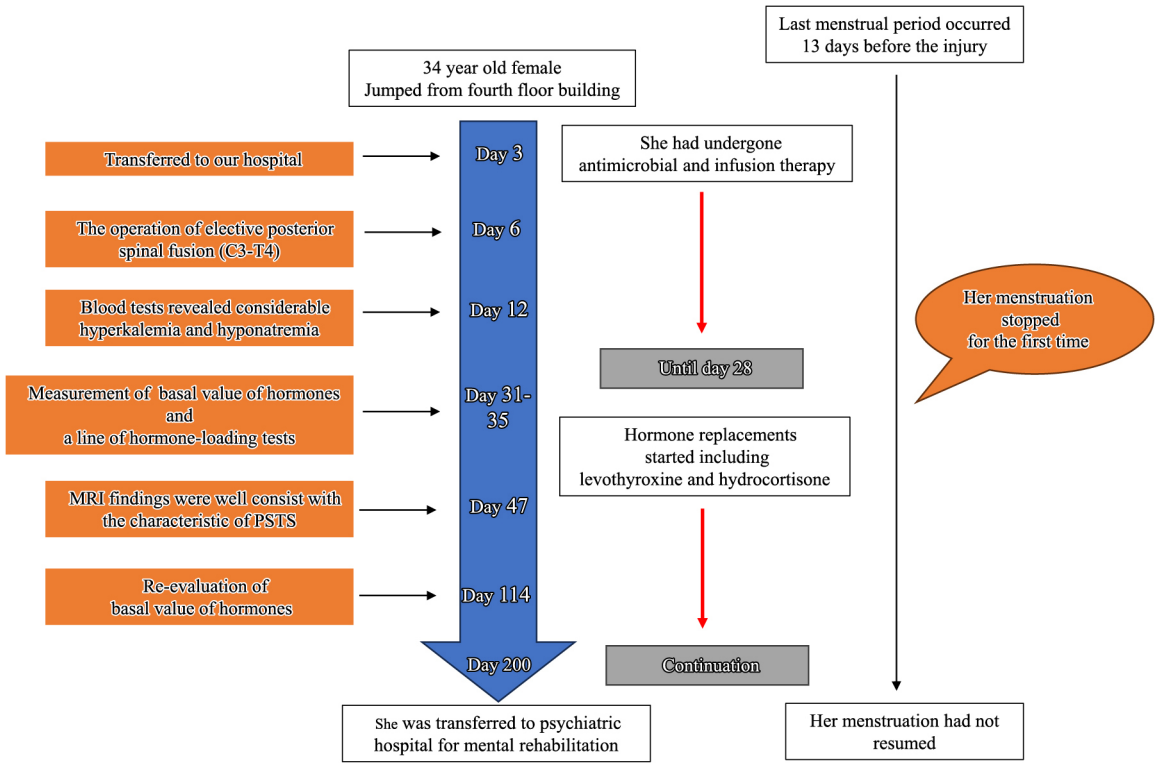

Fig. 3 The clinical course of the patient.
The timeline in this case is summarized based on the day of jumping.

had no history of severe head trauma, growth retardation, or delayed development of secondary sexual characteristics. In Fig. 4, we summarize the clinical manifestations and pathophysiological differences between PSTS and PSIS.

In our case, the normal ACTH response to the CRH test was combined with apparently low levels of basal ACTH and cortisol, while the cortisol response was diminished highly suggesting secondary adrenal insufficiency. In addition, the low level of peak cortisol after GHRP-2 administration also indicates secondary adrenal insufficiency [14]. A peak value of cortisol <15 μg/dL in a rapid ACTH test indicates primary adrenal insufficiency in some cases. However, some patients with traumatic brain injury in the acute phase, just as in our case, are likely to exhibit an attenuated response of cortisol [15]. Taken together, along with the loss of the pituitary stalk on MRI imaging, a line of hormonal dysregulation seems to be attributed to the above the pituitary gland.

To the best of our knowledge, neither PSTS nor PSIS associated with acute traumatic spinal cord injury in adulthood have been reported. In Table 3, we summarize the clinical characteristics of previously reported cases of PSTS and PSIS with adrenal insufficiency in adulthood. As far as our search extended over approximately 20 years of case reports using PubMed with keywords including "pituitary transection syndrome or invisible pituitary stalk or ectopic posterior pituitary" and "adrenal insufficiency" and "adult or adulthood" and "case report," there were only five cases reported in literature. According to previous reports [16-18], more than 20 years had elapsed between the onset of PSTS or PSIS and their final diagnosis. In contrast, the diagnosis in our case was established only three months after the onset. The measurement of cortisol levels as a cause of the imbalance in circulating electrolytes facilitated the early diagnosis of PSTS.

Our report has several limitations. First, we could not perform a serial tetracosactide acetate stimulation test or insulin tolerance test, mainly because of both time constraints in clinical practice and the risk of post-traumatic epilepsy. However, most of the data, including intact aldosterone production and MRI imaging findings were highly suggestive of secondary adrenal insufficiency. Some researchers have suggested that post-traumatic hypopituitarism includes not only direct mechanical transection of the pituitary stalk but also neuroinflammation and vascular mechanisms of injury [19]. The pituitary gland is suspended on the stalk within the third ventricle, with hypophyseal vessels descending the stalk and supplying the anterior pituitary lobe *via* the latticework of the portal vessels. Such perforating vessels are

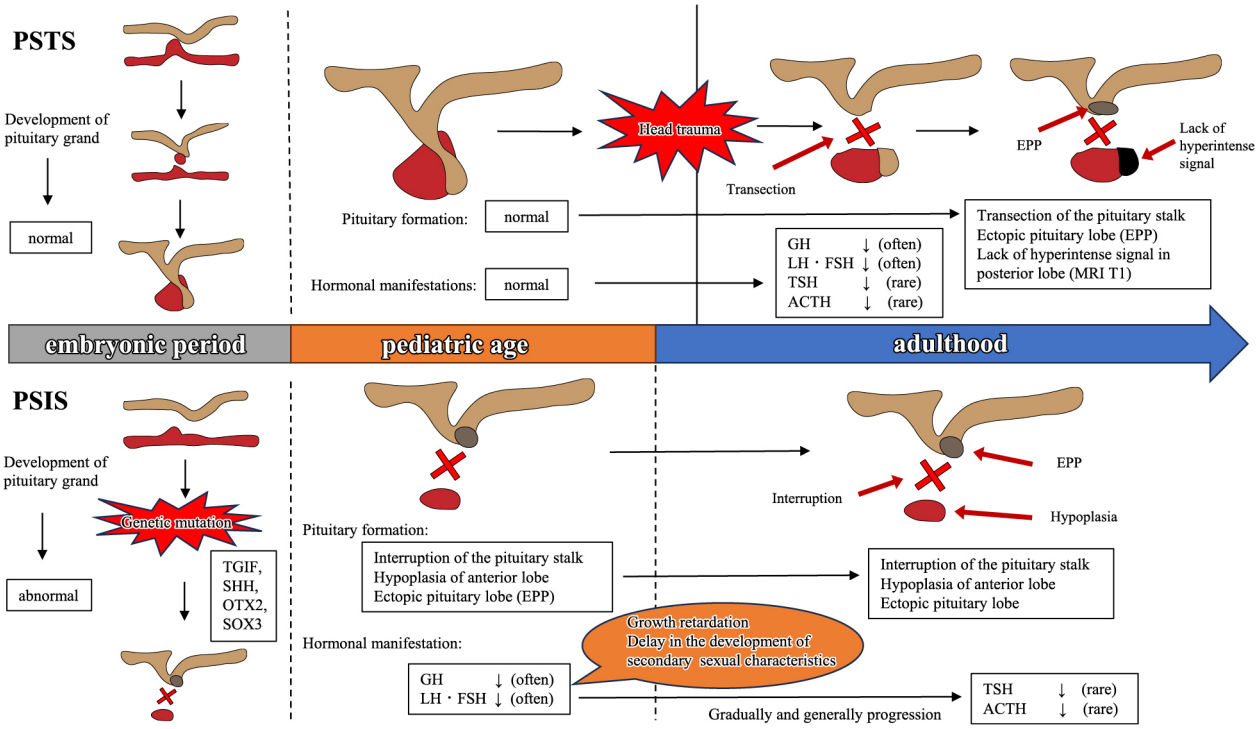

Fig. 4 Schematic representation of pathophysiological differences between post-traumatic pituitary stalk transection syndrome (PSTS) and pituitary stalk interruption syndrome (PSIS).

Schematic view of the clinical course of post-traumatic pituitary stalk transection syndrome (PSTS) and pituitary stalk interruption syndrome (PSIS). Hormonal manifestations of PSTS are temporally associated to head trauma. Alternatively, the clinical manifestations of PSIS include permanent deficiencies in anterior pituitary hormones, particularly growth hormone and gonadotropin during the pediatric age, which appear gradually but steadily progresses to panhypopituitarism in adulthood.

Table 3 Characteristics of previously reported five patients with PSTS and PSIS with adrenal insufficiency

	Sex	Age of diagnosis	Caused	Decreased levels of hormone	MRI findings
Ioachimescu AG *et al.* [16]	female	20	Head trauma at 2 months of age	Somatomedin C, LH, FSH, TSH, Cortisol	Loss of the pituitary stalk Hypoplasia of anterior lobe EPP at the infundibular recess
	male	19	unknown	Somatomedin C, LH, FSH, TSH Cortisol	Loss of the pituitary stalk Hypoplasia of anterior lobe EPP at posterior optic chiasm
	female	36	Breech delivery	Somatomedin C, LH, FSH, TSH, ACTH, Cortisol	Loss of the pituitary stalk Absence of anterior lobe EPP at floor of the hypothalamus
Gotyo N *et al.* [17]	male	38	Breech delivery	Somatomedin C, LH, FSH, TSH, ACTH, Cortisol	Loss of the pituitary stalk Normal size of anterior lobe EPP at the infundibulum
Makino S *et al.* [18]	male	48	Breech delivery	Somatomedin C, TSH, ACTH, Cortisol	Loss of the pituitary stalk Hypoplasia of anterior lobe EPP at the median eminence

Abbreviations: PSTS, post-traumatic pituitary stalk transection syndrome; PSIS, pituitary stalk interruption syndrome; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; ACTH, Adrenocorticotropic hormone; TSH, Thyroid-stimulation hormone; EPP, ectopic posterior pituitary gland.

vulnerable to shearing injuries from sudden acceleration-deceleration forces. Sudden transection of the pituitary stalk results in infarction of the anterior pituitary lobe [20]. A previous study demonstrated that anti-pituitary antibodies are commonly positive after traumatic brain injury and are associated with pathophysiology of hypopituitarism [21]. Taken together, it tempts us to speculate that diminished response of cortisol in the rapid ACTH test may be attributed to a consequence of the infarction and neuroinflammation in the anterior pituitary lobe due to the complete transection of the pituitary stalk. Infarction and neuroinflammation in the anterior pituitary lobe are likely to rapidly decrease ACTH production and release in the anterior pituitary lobe.

In conclusion, our case highlights endocrinological landscape of transection of the pituitary stalk by acute trauma.

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Disclosure

None of the authors has any potential conflicts of interest associated with this case report. Hiroaki Masuzaki is a member of *Endocrine Journal*'s Editorial board.

Author's Contribution

All the authors contributed to this work. Data collection was undertaken by Y.I. The draft of the manuscript was written by Y.I., A.T., K.H., K.Y., T.Y., T.T., M.U., Y.N., R.C., T.U., S.N., S.O. and H.M. reorganized the final form of the manuscript. All the authors read and approved the final version of the manuscript.

Informed Consent

Informed consent was obtained from the patient publication of this case report, and any accompanying data and images.

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