

Autoimmune polyendocrinopathy and hypophysitis after Puumala hantavirus infection

Marlene Tarvainen¹, Satu Mäkelä^{1,2}, Jukka Mustonen^{1,2} and Pia Jaatinen^{1,2,3}

¹School of Medicine, University of Tampere, Tampere, Finland, ²Department of Internal Medicine, Tampere University Hospital, Tampere, Finland, and ³Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

Correspondence
should be addressed
to P Jaatinen

Email
pia.jaatinen@uta.fi

Summary

Puumala hantavirus (PUUV) infection causes nephropathia epidemica (NE), a relatively mild form of haemorrhagic fever with renal syndrome (HFRS). Hypophyseal haemorrhage and hypopituitarism have been described in case reports on patients with acute NE. Chronic hypopituitarism diagnosed months or years after the acute illness has also been reported, without any signs of a haemorrhagic aetiology. The mechanisms leading to the late-onset hormonal defects remain unknown. Here, we present a case of NE-associated autoimmune polyendocrinopathy and hypopituitarism presumably due to autoimmune hypophysitis. Thyroid peroxidase antibody seroconversion occurred between 6 and 12 months, and ovarian as well as glutamate decarboxylase antibodies were found 18 months after acute NE. Brain MRI revealed an atrophic adenohypophysis with a heterogeneous, low signal intensity compatible with a sequela of hypophysitis. The patient developed central (or mixed central and peripheral) hypothyroidism, hypogonadism and diabetes insipidus, all requiring hormonal replacement therapy. This case report suggests that late-onset hormonal defects after PUUV infection may develop by an autoimmune mechanism. This hypothesis needs to be confirmed by prospective studies with sufficient numbers of patients.

Learning points:

- Pituitary haemorrhage resulting in hypopituitarism has been reported during acute HFRS caused by PUUV and other hantaviruses.
- Central and peripheral hormone deficiencies developing months or years after HFRS have also been found, with an incidence higher than that in the general population. The pathogenesis of these late-onset hormonal defects remains unknown.
- This case report suggests that the late-onset hypopituitarism and peripheral endocrine defects after HFRS could evolve via autoimmune mechanisms.
- The sensitivity of current anti-pituitary antibody (APA) tests is low. A characteristic clinical course, together with typical brain MRI and endocrine findings may be sufficient for a non-invasive diagnosis of autoimmune hypophysitis, despite negative APAs.

Background

Hantaviruses cause haemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus cardiopulmonary syndrome (HCPS) in the Americas (1).

Puumala hantavirus (PUUV) causes a mild HFRS called nephropathia epidemica (NE). In Finland, annually 1000–3000 cases of NE are serologically diagnosed. The

Table 1 Basic laboratory test results during acute nephropathia epidemica and at the 1-month follow-up visit.

Parameter	Lowest level at hospital	Highest level at hospital	At discharge	At 1-month follow-up	Reference range
WBC (10 ⁹ /L)	5.5	45	5.8	6.8	3.4–8.2
Platelet count (10 ⁹ /L)	5	207	207	260	150–360
Haemoglobin (g/L)	90	202	97	114	117–155
CRP (mg/L)	8.7	57.4	8.7	<1	0–10
ALT (U/L)	13	35	13	N/A	10–45
Creatinine (µmol/L)	206	891	206	89	50–90
Urea (mmol/L)	12.9	35.2	12.9	N/A	2.6–6.4
Potassium (mmol/L)	3.7	5.1	3.9	N/A	3.3–4.8
Sodium (mmol/L)	121	132	130	N/A	137–144

ALT, alanine transaminase; CRP, C-reactive protein; N/A, not assessed; WBC, white blood cells.

typical features of NE are increased capillary permeability, renal involvement and thrombocytopenia, the latter rarely causing serious haemorrhages (1). The patients commonly suffer from high fever, headache, reduced visual acuity, abdominal pain, nausea and backache (1).

Hypophyseal haemorrhage and panhypopituitarism have been described in case reports on patients with NE (2, 3, 4, 5, 6, 7, 8). Defects of the gonadal and/or thyroid axis have been found in more than half of the patients during the acute phase of NE (9). We have also reported chronic hypopituitarism in 5 of 54 patients, primary hypothyroidism in 5 patients and chronic subclinical testicular failure in 5 of 37 men during a median follow-up of 5 years after NE (9). Chronic hypopituitarism was also identified in 18% of patients

with a previous HFRS in a retrospective Serbian study of 60 adults who had recovered from HFRS years ago (10). Thus, patients with HFRS may be at high risk of developing hypopituitarism or peripheral hormone deficiencies later on (8, 9, 10). However, no obvious late-onset hypopituitarism was diagnosed in a cohort of 47 patients re-examined 4–8 years after NE in Northern Finland (11). The pathophysiological mechanisms of hypopituitarism developing as a late complication of NE remain unclear.

We present a patient who developed an autoimmune polyendocrine syndrome and hypopituitarism possibly due to autoimmune hypophysitis six to twelve months after the acute NE. We also review previous case reports on HFRS-induced hypopituitarism.

Table 2 Summary of the hormonal test results during acute NE and at the follow-up visits.

Variables (units)	Acute NE	1-month follow-up	6-month follow-up	12-month follow-up	24-month follow-up	Reference range
ft4 (pmol/L)	10.7	7.7	7.8	18.1 ¹	16.7 ¹	11.0–22.0
TSH (mU/L)	9.1	0.64	4.1	<0.01 ¹	0.25 ¹	0.27–4.2
Oestradiol (nmol/L)	1.09	0.04	<0.02	0.17 ²	0.17 ²	*
FSH (U/L)	3.0	2.8	4.1	1.5 ²	1.7 ²	*
LH (U/L)	12.2	0.9	1.5	0.8 ²	1.5 ²	*
GH (mU/L)	59.4	0.5	0.5	0.3	0.33	0.0–11.0
IGF-1 (nmol/L)	13	17	12	16	9**	12–46 10–37**
Cortisol (nmol/L)	1284	277	356	253	249**	180–680 170–500**
ACTH (ng/L)	12	11	19	20	10	0.0–46.0
PRL (mU/L)	439	366	256	283	240	102–496
TPOAb (kU/L)	<5	13	23	85	66	<34

¹On levothyroxine substitution, ²on oestrogen–progesterone substitution, *oestradiol, FSH and LH values were evaluated according to the phase of the menstrual cycle, **IGF-1 and cortisol laboratory test methods changed during the follow-up. The new reference ranges and the values measured with the new methods are marked with asterisks (**).

Case presentation

A 25-year-old previously healthy woman presented with fever of 39°C, oliguria and lower back pain. At presentation, the plasma C-reactive protein (CRP) concentration was 39 mg/L and urinalysis revealed proteinuria (+++) and haematuria (++) . Pyelonephritis was suspected, and she was admitted to a ward in the primary health care centre. Intravenous cefuroxime was started. The patient began to suffer from nausea, vomiting, and visual disturbances, and she was transferred to Tampere University Hospital. NE was suspected, and a point-of-care anti-PUUV antibody test (Reascan Puumala IgM, Reagent International, Toivala, Finland) was returned positive. The patient was anuric and hypotensive, and i.v. fluids were administered. During the next few days, she experienced headache and dizziness. Diuresis restarted on day six after the onset of fever. The highest daily urinary output was 3700 mL in the polyuric phase. The mild headache was cured by paracetamol and the visual disturbances soon subsided. The patient was discharged 14 days after admission.

Investigations

The diagnosis of NE was verified by high levels of specific anti-PUUV IgM and IgG antibodies. Other laboratory findings (Table 1) typical of NE included severe thrombocytopenia, leukocytosis and elevated plasma creatinine and urea concentrations, as well as proteinuria and haematuria. On the first few days of hospitalisation, serum levels of cortisol and growth hormone (GH) were high, and free thyroxine (fT4) was low (Table 2).

Outcome and follow-up

The patient participated in a prospective study of the hormonal consequences of NE, and written informed consent was obtained. At the first follow-up visit one month after the acute illness, the patient was slightly anaemic, but other laboratory findings were normal (Table 1). She still had fatigue and an irregular menstrual cycle. Three months after the NE, the patient started to suffer from hot flushes, mild headache, sleeping disorders, oedema and amenorrhoea. Six months after the acute illness, central hypothyroidism and hypogonadotropic hypogonadism were detected (Table 2). There were no symptoms or laboratory findings compatible with diabetes insipidus (DI). Levothyroxine and oestrogen–progesterone replacement therapy were started.

Brain magnetic resonance imaging (MRI, 3 Tesla) was performed 9 months after the acute NE and showed an atrophic adenohypophysis with a heterogeneous, low signal intensity, compatible with a sequela of hypophysitis (Fig. 1). There were no signs of haemorrhage, tumours or other abnormal findings on the MRI scan.

At the 12-month follow-up visit, the patient reported constipation, abnormal thirst, polyuria and loss of appetite. The laboratory tests showed high plasma sodium level (145 mmol/L). DI was suspected, and a therapeutic trial with desmopressin p.o. was commenced. Desmopressin substitution (60 µg b.i.d.) corrected the polyuria and other symptoms and normalised the plasma sodium concentration.

Plasma thyroid peroxidase antibody (TPOAb) levels were normal during acute NE and at one-month and six-month follow-up visits, but increased by the 12-month follow-up visit (Table 2). Due to the clinical signs of DI

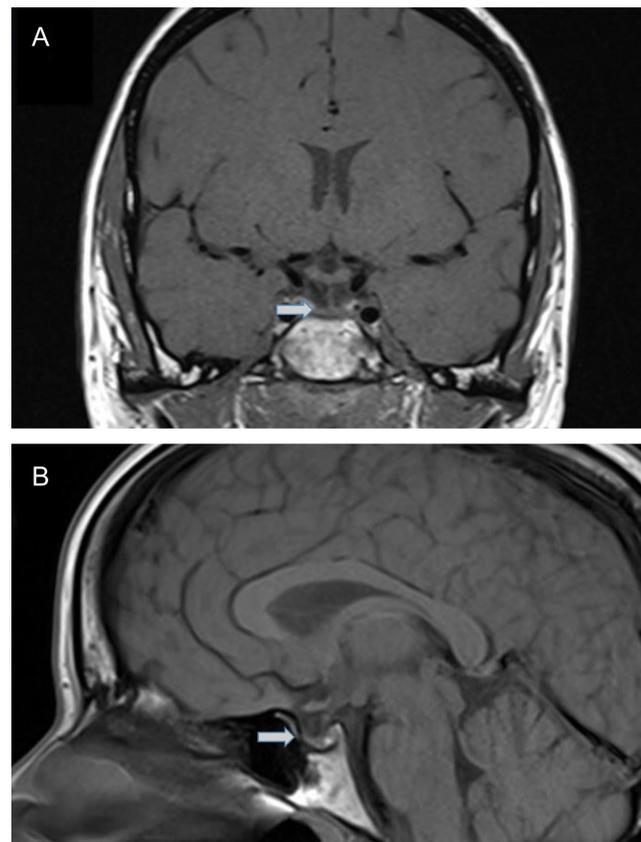


Figure 1
Brain MRI scan (T1-weighted) 9 months after the acute NE, showing an atrophic adenohypophysis (arrow) with a heterogeneous, low signal intensity, compatible with a sequela of hypophysitis. (A) Coronal plane. The height of the hypophysis is 2 mm. (B) Sagittal plane. The patient developed diabetes insipidus later on, but at this point, the 'bright spot' is still visible in the posterior pituitary.



Table 3 Summary of previous case reports on HFRS-related panhypopituitarism.

Study	Type of hormonal deficiency					Time from HFRS to hypopituitarism	Radiological or histological findings (imaging modality)	Follow-up time	Hormonal recovery
	ACTH	TSH	LH/FSH	GH*	AVP				
Forslund <i>et al.</i> (2)	x	x	x	N/A	–	15 years	Empty sella (CT)	N/A	No
Settergren <i>et al.</i> (5)	x	x	x	x ^{a,c}	–	6 mo	–	N/A	No
Suh <i>et al.</i> (14)	x	x	x	x ^c	N/A	3 mo	Haemorrhage, later atrophy (MRI)	3 mo	No
Park and Pyo (15)	x	x	x	x ^c	N/A	Acute	–	N/A	N/A
Kim <i>et al.</i> (16)	x	x	N/A	x ^c	N/A	13 years	–	1 mo	No
Hautala <i>et al.</i> (3)	x	x	x	N/A	N/A	5 mo	Acute: Enlarged pituitary gland, haemorrhage	10 mo	No
	x	x	x	–	N/A	Acute	Acute: Enlarged pituitary gland, haemorrhage	2 mo	No
							2 mo: Decreased pituitary gland size and partial resorption of haemorrhage (MRI)		
Sane and Färkkilä (4)	x	x	x	x ^b	–	10 mo	Decreased pituitary enhancement (CT)	17 mo	No
Pekic <i>et al.</i> (8)	x	x	x	x ^{a,b,c}	N/A	1.5 years	Atrophy, empty sella (MRI)	N/A	No
	x	x	x	x ^{a,b,c}	N/A	2 years		1 mo	No?
	x	x	x	x ^b	N/A	2 years		15 days	No?
Jost <i>et al.</i> (6)	x	x	x	N/A	N/A	Acute	Acute: Enlarged pituitary gland	5 mo	Partial**
							5 mo: Normal (MRI)		
Sarigüzel <i>et al.</i> (17)	x	x	x	x ^b	–	Acute	Haemorrhage, atrophy (MRI)	16 mo	No
Kaybas <i>et al.</i> (18)	x	N/A	x	–	N/A	Acute	Normal (MRI)	N/A	N/A

ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; d, days; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; mo, months; N/A, data not available; TSH, thyroid-stimulating hormone; y, years.

*GH/IGF-1 axis deficiency was diagnosed by determining ^aserum GH level, or ^bserum IGF-1 level or by conducting a ^cGH axis stimulation test.

**Adrenocortical and thyroid axis recovered, and gonadal axis did not.



and brain MRI findings, hypophysitis was suspected and further etiological investigations were scheduled. Serum calcium, angiotensin-converting enzyme, lysozyme, antinuclear antibody (ANA) and IgG4 levels were normal. Anti-pituitary antibodies (APA) were measured by a line blot and a radioimmuno-precipitation assay (MVZ Laboratory Dr Volkmann and Colleagues, Karlsruhe, Germany), and the tests yielded normal results. Glutamate decarboxylase antibody (GADAb 892.7IU/mL, reference <10IU/mL), TPOAb (53kU/L, reference <34kU/L) and ovarian antibody (OvarAb titer 10, reference <1) tests were all positive. The anti-adrenal antibody (AdrAb) titre was normal (<1). The GADAbs were measured by an enzyme immunoassay (Euroimmune anti-GAD-ELISA, Luebeck, Germany), whereas the OvarAbs and the AdrAbs were measured by indirect immunofluorescence (PhD 1xSystem, Bio-Rad Laboratories) on sections of primate ovary and adrenal gland respectively, at the certified Huslab Laboratories, Helsinki, Finland. Other measurements were performed by the routine laboratory methods of the certified Fimlab Laboratories, Tampere, Finland.

At the latest visit, 2 years after NE, the patient was asymptomatic on desmopressin, L-thyroxine and oestrogen–progesterone substitution. Despite the oestrogen substitution, the IGF-1 level was borderline low and cortisol was in the low normal range (Table 2). The follow-up is continued at the Endocrinology Outpatient Clinic.

Discussion

To our knowledge, this is the first case reported with autoimmune polyendocrinopathy and hypopituitarism developing soon after acute NE. Our patient started to suffer from symptoms suggestive of hormonal deficiencies three months after the NE. Laboratory tests revealed hypopituitarism six months after the discharge from hospital. Partial DI was diagnosed one year after NE. Nine months after the NE, brain MRI showed atrophy of the adenohypophysis with a heterogeneous, low signal intensity, compatible with a sequela of hypophysitis. Autoantibodies emerged during the first 18 months after the NE. The APAs were negative, but the diagnostic sensitivity and specificity of APA tests are known to be low (12, 13).

Previously, only one case report has been published on NE-associated hypophysitis (6). The patient had transient panhypopituitarism, requiring hormonal replacement therapy with L-thyroxine and hydrocortisone during the acute NE. In contrast with the present case, the hormone levels soon normalised with the resolution of

the acute PUUV infection and remained normal during the follow-up of 5 months. In that case report, brain MRI showed enlargement of the pituitary gland, but no pituitary haemorrhage or necrosis and no hypothalamic alterations (6). Both the clinical course and the radiological characteristics of the previous case suggest a direct effect of the viral infection, rather than an autoimmune mechanism, causing the transient pituitary defect.

Table 3 summarises eleven previous case reports (2, 3, 4, 5, 6, 8, 14, 15, 16, 17, 18) with 14 well-characterised cases of HFRS-related panhypopituitarism. Five patients were diagnosed with hypopituitarism requiring chronic hormonal replacement, starting from the acute phase of HFRS (3, 6, 15, 17, 18). Nine patients developed late-onset panhypopituitarism months or years after HFRS (2, 3, 4, 5, 8, 14, 16). A lethal case of hypophyseal haemorrhage during acute NE was also reported (3). In addition to the cases of panhypopituitarism represented in Table 3, we found five cases of chronic hypogonadotrophic hypogonadism, two with central hypothyroidism and three isolated ones, in the previous retrospective analysis of 54 NE patients (9). In the retrospective series of 60 patients with previous HFRS, there were six cases of a single pituitary hormone deficit and five cases of multiple pituitary hormone deficiencies respectively (10).

The pathophysiology of chronic hormone deficiencies after HFRS is still unclear. Viral infections have been linked to the pathogenesis of several autoimmune diseases. For example, many viruses such as enteroviruses have been associated with type 1 diabetes (19). It is possible that an acute PUUV infection may affect the pituitary and peripheral endocrine glands, as well as the immune system, enhancing the production of autoantibodies against the endocrine organs. In our patient, TPO seroconversion appeared between 6 and 12 months after NE. Measured 18 months after HFRS, TPO, ovarian and GAD antibody tests were all positive.

Several lines of evidence suggest that primary hypophysitis may develop by an autoimmune mechanism (12, 20). Pregnancy and childbirth are known risk factors for hypophysitis. Lymphocytic hypophysitis is commonly associated with autoimmune diseases, such as Hashimoto's thyroiditis, Graves' disease, Addison's disease, type 1 diabetes, atrophic gastritis and Sjögren's syndrome. Such an association has been reported in 25–50% of the cases (12, 20).

Hypopituitarism is the most common presentation of autoimmune hypophysitis. The typical order of trophic hormone deficiency has been reported as ACTH>TSH>FSH/LH>PRL>GH (12). However, the recent report with 76 cases



from Germany found hypogonadotrophic hypogonadism, the most frequent hormonal defect in primary hypophysitis (13). Our patient first started to experience symptoms suggestive of hypogonadism, three months after NE. Central hypothyroidism and hypogonadotrophic hypogonadism were diagnosed six months after the acute NE, and hormonal substitutions were started. Her cortisol levels have been in the low normal range, which is likely to reflect an impaired cortisol production, in view of the oestrogen replacement therapy increasing the cortisol-binding globulin concentration.

At the acute phase of hypophysitis, a sellar mass effect may develop, provoking headache, diplopia and visual field deficits. Infundibular or posterior pituitary defects may cause antidiuretic hormone (ADH and vasopressin) deficiency and central DI, presenting with polyuria and polydipsia in 20–48% of patients with autoimmune hypophysitis (12). In most cases of hypophysitis, the level of PRL is normal or even low (21), as in our patient. During the anuric phase of acute NE, the patient had hyponatraemia. Fluid retention associated with acute kidney injury was probably an important cause of low sodium concentration at that time. Nevertheless, hyponatraemia might also be caused by excessive secretion of ADH, i.e. an acute SIADH. The partial DI of the patient, diagnosed one year after NE, reflected a slight defect of the hypothalamic-infundibulo-neurohypophyseal system, as the intense signal of the posterior pituitary was still visible on MRI, and there was no visible pathology in the infundibulum or the hypothalamus, 3 months before the diagnosis of DI.

The brain MRI of our patient revealed an atrophic adenohypophysis with a heterogeneous, low signal intensity nine months after acute NE. These findings are compatible with a sequela of hypophysitis (12). Haemorrhage may also cause atrophy of the adenohypophysis (13). However, our patient presented no symptoms or clinical findings indicative of hypophyseal haemorrhage either during acute NE or during the follow-up. A definitive diagnosis of hypophysitis requires histological verification from a biopsy specimen, but a characteristic clinical course, together with typical MRI and hormonal findings have been suggested to suffice for a non-invasive diagnosis (12, 13). Distinctive radiological features in acute autoimmune hypophysitis are symmetric enlargement of the pituitary gland, homogenous post-gadolinium enhancement, thickened infundibulum in the midline, loss of posterior 'bright spot' on T1 imaging and intact sellar floor (12, 22). A central hypointensity, representing necrosis or cyst formation, has been reported in up to one-third of the patients (13, 21). At later stages

of hypophysitis, pituitary atrophy and empty sella are typical findings on MRI (12).

Circulating anti-pituitary autoantibodies (APA) may be detected in autoimmune processes of the pituitary gland. The low diagnostic sensitivity and specificity of present APA tests unfortunately limit their diagnostic utility (12, 20). The present patient was negative for APAs, but the clinical picture and the presence of several other autoantibodies make autoimmune hypophysitis a plausible cause of her hypopituitarism. A direct effect of the PUUV infection, increased capillary permeability or a minor haemorrhagic damage are other possible mechanisms that may have led to the pituitary atrophy and panhypopituitarism observed.

In conclusion, we report the first case of NE-associated autoimmune polyendocrinopathy and a possible autoimmune hypophysitis. An autoimmune mechanism could explain the late-onset hypopituitarism that has been reported to develop months or years after HFRS (8, 9, 10). Autoimmune inflammation could also explain the insufficiencies of peripheral hormonal glands, which seem to be more frequent after NE than in the general population (9). The case reports and retrospective cohorts published so far call for prospective studies, to clarify the epidemiology and the mechanisms of hormonal deficiencies after NE and other types of HFRS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for the publication of the submitted article and accompanying images.

Author contribution statement

Dr Marlene Tarvainen examined the patient during acute NE and at the follow-up visits and drafted the manuscript. Dr Satu Mäkelä and Prof Pia Jaatinen were involved in the treatment of the patient and contributed to the writing of the manuscript. Prof Jukka Mustonen contributed to manuscript writing and editing.

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