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Hypopituitarism in a Dengue Shock Syndrome Survivor without known Pituitary Adenoma

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Abstract. Dengue infection is endemic in South East Asia and parts of the Americas. Dengue hemorrhagic fever is characterized by vascular permeability, coagulation-disorders and thrombocytopenia, which can culminate in hypotension i.e. dengue shock syndrome. Hypopituitarism arising as a complication of dengue is extremely rare. Hemorrhagic pituitary apoplexy of pre-existing pituitary adenomas has been rarely reported in dengue. We describe an uncommon case of hypopituitarism in a dengue shock syndrome survivor without known pituitary adenoma. A 49 years old nulliparous lady (from Kuala Lumpur, Malaysia) presented with typical symptoms of hypocortisolism. Postural hypotension was evident with normal secondary sexual characteristics. Further history revealed that she survived an episode of dengue shock syndrome 6 years ago where premature menopause developed immediately after discharge, and subsequently insidious onset of multiple hormonal deficiencies indicative of panhypopituitarism. There were no neuro-ophthalmological symptoms suggestive of pituitary apoplexy during hospitalization for severe dengue. Magnetic resonance imaging of the pituitary 6 years later revealed an empty sella. Autoimmune screen and anti-thyroid peroxidase antibodies were negative. We describe a rare possible causative association of severe dengue with panhypopituitarism without known pituitary adenoma, postulating pituitary infarction secondary to hypotension (mimicking Sheehan's syndrome), or a direct viral cytopathic effect. Subclinical pituitary apoplexy secondary to asymptomatic pituitary hemorrhage however cannot be excluded. Future research is required to determine the need for and timing of pituitary axis assessment among dengue shock syndrome survivors.

INTRODUCTION

Dengue fever (DF), an arboviral illness, is a major public health concern world-wide. The annual worldwide incidence of dengue was 50 million, of which majority was from Asia [WHO, 2011]. The endothelium is the target of immune pathological mechanisms in dengue [WHO, 2011]. Dengue hemorrhagic fever (DHF), is characterized by vascular permeability and coagulation disorders/ thrombocytopenia, which can culminate in hypotension i.e. dengue shock syndrome (DSS) [WHO, 2011]. Dengue is rarely associated with hypopituitarism. There have been five published reports linking dengue with pituitary pathology [Vastrad *et al*., 2010; Kumar *et al*., 2011; Wildemberg *et al*., 2012; Mishra *et al*., 2014; Tan *et al*., 2014]. Four were associated with hemorrhage into a pre-existing pituitary adenoma, presenting as classic pituitary apoplexy [Kumar *et al*., 2011; Wildemberg *et al*., 2012; Mishra *et al*., 2014; Tan *et al*., 2014]. Four publications reported evidence of hypopituitarism [Vastrad *et al*., 2010; Kumar *et al*., 2011; Wildemberg *et al*., Tan *et al*., 2014], however the case described by Mishra *et al* had no evidence of hormonal

insufficiency [Mishra *et al.*, 2014]. Here, we described a case of DSS in a subject without known pituitary adenoma, complicated by empty sella syndrome (ESS).

CASE REPORT

A 49 years old nulliparous lady with a history of hypertension presented with 3 months history of easy fatiguability and postural giddiness in December 2014. She denied having headache, visual loss or past head trauma. Menstrual cycles were regular till a hospitalization for DF 6 years prior where premature menopause (aged 43) developed immediately post discharge. She was not on sex hormone replacement and denied complementary medicine or glucocorticoid consumption. Three years ago a general practitioner diagnosed her with hypothyroidism commencing levothyroxine replacement. However, she had self-ceased levothyroxine for 3 months. There were no symptoms of autoimmune disorders.

Clinical examination revealed an obese lady [body-mass-index: 35 kg/m^2]. Her temperature was 36.6^{o}C, heart-rate (HR) 68 beats/minute with random-blood-glucose of 81mg/dL (4.5mmol/L). Postural hypotension was evident with lying blood pressure (BP) 134/72mmHg and standing BP 124/60mmHg. Secondary sexual characteristics and visual fields on confrontation were normal. She was clinically euthyroid. There were no signs of autoimmune diseases. Biochemistry confirmed panhypopituitarism with an apparent empty sella on MRI pituitary (Table 1). Anti-thyroid peroxidase antibodies, complement studies and autoimmune screen were negative. Dengue IgG was positive.

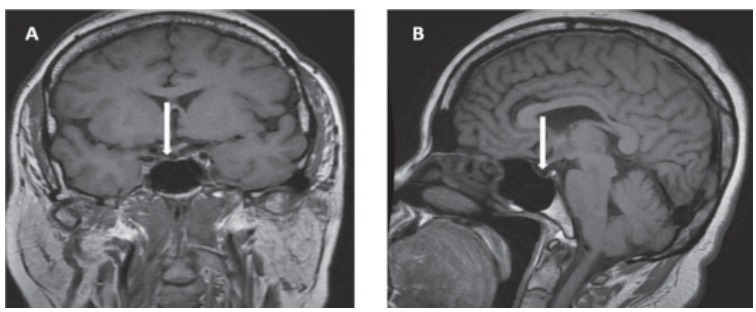
Her admission details 6 years ago in another centre were reviewed and confirmed on the DSS episode. She was hospitalized with 3 days history of fever, myalgia, vomiting and abdominal pain associated with thrombocytopenia (albeit without history of overt bleeding). Her vital signs at presentation were BP 117/69mmHg, HR 88 beats/min and temperature 37°C. A presumptive diagnosis of DF in critical phase with warning signs was made. Two days after admission (day 6 of illness), she became hypotensive (98/60mmHg), tachycardic (HR 100 beats/min) with low pulse volume. Clinical assessment and chest radiograph confirmed bilateral pleural effusion indicating plasma leakage characteristic of severe dengue. Her hematocrit had risen from 37.6% to 43.3%. A diagnosis of DSS was made based on: a) presence of plasma leakage (pleural effusion, hemoconcentration); b) hypotension; c) rapid and weak peripheral pulses. After fluid resuscitation of 20ml/kg in one hour, she remained tachycardic with HR 96 beats/min and low pulse volume, although BP improved to 112/55mmHg. She was given another fluid bolus of 10ml/kg in two hours and transferred to the intensive care unit (ICU). Her vital signs stabilized after the 2nd fluid bolus. She was therefore maintained on 3ml/kg/hour crystalloid infusion for the subsequent two hours. Her fluid management and laboratory findings were summarized in Table 2. She was transferred to the general ward after 72 hours of ICU stay (day 9 of illness). Dengue IgM (day 4 of illness) was negative. A paired convalescent serum looking for a fourfold rise in IgM titres and dengue NS1 antigen were not sent. She did not have any headache/visual disturbances/altered consciousness indicative of pituitary apoplexy and did not require invasive ventilation or blood transfusion throughout admission. She was discharged on day 13 of illness with full recovery of her platelet count.

A retrospective diagnosis of ESS/panhypopituitarism secondary to DSS was made and the subject was commenced on oral hydrocortisone 10/5mg twice/day, levothyroxine 125mcg daily and combined estrogen/progesterone replacement. She remains well on hormone replacement and is now on regular follow up with an endocrinologist.

Table 1. Anterior Pituitary Hormone Profile in year 2014

FSH (IU/L)	< 1.0	Postmenopausal female: 23.0-116
LH (IU/L)	< 1.0	Menstruating Female: Follicular phase: 1.9-12.5 Midcycle peak: 8.7-76.3 Luteal phase: 0.5-16.9
Oestradiol (pmol/L)	100	Postmenopausal female: Not detectable – 118
8am serum cortisol (nmol/L)	41.4	7-9 am: 118.0 – 615.3
ACTH (pg/ml)	19.0	0 – 46.0
fT4 (pmol/L)	9.0	11.6 – 23.2
TSH (mIU/L)	1.92	0.55 – 4.78
Prolactin (mIU/L)	165.4	Postmenopausal female: 38.2 – 430.4
IGF-1 (ng/ml)	25.0	94.0 – 252.0
GH (ng/ml)	0.1	0.0 – 8.0

MRI Pituitary (T1-weighted)



A, B: Coronal and Sagittal views respectively. Arrows showed empty sella.

***Abbreviations**: FSH – Follicle stimulating hormone; LH – Luteinising hormone; ACTH – Adrenocorticotropin hormone; TSH – Thyroid-stimulating-hormone; fT4 – Free thyroxine; IGF-1 – Insulin-like growth factor-1; GH – Growth hormone.*

***Conversion factors**: To convert values for cortisol to mg/dL, divide by 27.59. To convert values for fT4 to ng/dL, divide by 12.87. To convert values for prolactin to µg/L, divide by 21.2.*

DISCUSSION

This case illustrated the important recognition of hypopituitarism post severe dengue in tropical countries. In our subject, history, examination and biochemical findings had excluded other causes of ESS.

Dengue infection is a self-limiting acute febrile illness characterized by thrombocytopenia, which is caused by one of the four dengue virus serotypes. Most patients recover uneventfully while a minority develop a severe sometimes fatal form known as DHF/DSS, characterized by increased vascular permeability and hemodynamic instability. Hypopituitarism as a complication of dengue is extremely rare, possibly under reported. The consequences of unrecognized hypocortisolism/hypothyroidism both acutely in DSS and

Table 2. Clinical Evaluation & Laboratory Results during Hospitalization for DSS in year 2009 (ICU stay from day 6 to day 9)

Variable	D4	D6	D7	D9	D10	D11	D13
Clinical							
T (°C)	37	37.5	37.5	37	37	37	37
RR (breath/min)	20	ND	ND	ND	ND	ND	ND
S_aO_2 (%)	98	98	ND	98	100	100	100
O_2 (L/min)	RA	RA	3	RA	RA	RA	RA
HR (beats/min)	88	96	100	100	86	86	88
BP (mmHg)	117/69	120/82	98/61	124/67	128/75	124/72	139/77
Fluids							
Intravenous fluids (ml/kg/hr)	1	2	20ml/kg x 1 cycle, 10ml/kg x 1 cycle, then maintained at 3ml/kg	1	Nil	Nil	Nil
Laboratory Values							
Hb (g/dL)	13.7	15.6	16.2	12.1	10.9	10.5	11.6
HCT (%)	37.6	43.3	44.5	34.3	33.8	30.0	32.5
WC (x10^9/L)	1.93	2.61	3.56	6.73	5.66	4.47	4.71
PLT (x10^9/L)	19	19	12	28	49	107	234
ALT (U/L)	35	ND	58	62	55	46	34
Alb (g/L)	27	ND	23	20	26	30	38
Urea (mmol/L)	3.0	4.0	2.0	1.0	0.6	0.4	0.3
Creat (µmol/L)	53	62	53	44	44	45	40

Abbreviations: *D – day of illness; ND – not documented; T – temperature; RR – respiratory rate; S_aO_2 – Arterial oxygen saturation; O_2 – Oxygen; RA – room air; Hb – Hemoglobin; HCT – Hematocrit; WC – White cells; PLT – Platelets; ALT – alanine transaminase; Alb – Albumin; Creat – Creatinine; Sec – Second.*
Normal values: *Alanine transaminase 7-35 U/L, albumin 35-55 g/L, urea 2.5-8.0 mmol/L, creatinine 62-124 µmol/L.*
Conversion factors*: To convert values for urea to mmol/L, multiply by 0.357. To convert values for creatinine to µmol/L, multiply by 88.4.*

chronically after discharge can be lethal. Our subject's unusual presentation indicates the need to further explore the possibility that hypopituitarism is rare sequelae of DSS.

Postulated mechanisms of hypopituitarism post-dengue in our subject are: 1) subclinical pituitary apoplexy (PA) of a normal pituitary gland; 2) ischemia of a normal pituitary gland secondary to hypotension; and 3) necrosis of the pituitary gland secondary to direct cytopathic effect of the dengue virus. Our nulliparous subject had no clinical history, biochemical and imaging evidence suggestive of a pre-existing pituitary tumour or hypopituitarism prior to DSS. There was a clear temporal association of amenorrhoea with the DSS admission and progressive, sequential, insidious onset of hypothyroidism and hypocortisolism. MRI confirmed ESS 6 years later. Only one other case report by Vastrad *et al.*, had described ESS, without known pre-existing pituitary adenoma, hypothesizing pituitary infarction secondary to dengue associated hypotension [Vastrad *et al.*, 2010]. It is however possible that their 75 years old male subject had prior undiagnosed hypopituitarism that was unmasked post-dengue, as there was an atypical/subacute presentation of hypopituitarism over 2 weeks rather than the more classical insidious onset over years seen in our subject [Vastrad *et al.*, 2010].

Our subject's panhypopituitarism may have resulted from subclinical PA secondary to asymptomatic hemorrhage into a normal pituitary gland consequent to thrombocytopenia or increased microvascular permeability associated with DHF/DSS [Glezer *et al.*, 2015]. PA is characterized by acute infarction or hemorrhage of the pituitary gland (usually within a pre-existing

tumour) that results in necrosis or sudden increase in gland volume [Glezer *et al*., 2015]. While PA has a predilection for non-functioning pituitary macroadenomas and macroprolactinomas, it can rarely occur in microadenomas, a non-adenomatous gland and even normal pituitary gland as perhaps in our subject [Vastrad *et al*., 2010; Glezer *et al*., 2015]. Acute hemorrhage into the pituitary gland can be the only bleeding site in DHF as was seen in the afore-mentioned four cases of PA in pre-existing pituitary macro-adenomas [Kumar *et al*., 2011; Wildemberg *et al*., 2012; Mishra *et al*., 2014; Tan *et al*., 2014]. These published reports presented with classical symptoms of PA and pituitary hemorrhage on MRI that eventually required neurosurgical decompression [Mishra *et al*., 2014; Tan *et al*., 2014]. Our subject differs from these cases, as she denied any symptoms of PA during her dengue admission. Neither did she have symptoms suggesting a pituitary tumour before hospitalization (irregular menses/headache/visual field defects), thus making undiagnosed pre-existing pituitary adenoma or prior idiopathic hypopituitiarism less likely. Subclinical PA, on the other hand, is characterized by asymptomatic pituitary hemorrhage detected only on imaging [Glezer *et al*., 2015]. These patients can present with ESS on MRI upon late presentation (6 years post-infection in our subject) [Glezer *et al*., 2015].

We postulate that the most likely cause of panhypopituitarism in our subject was a pituitary infarction secondary to the hypotension/BP oscillations typical of DSS. The anterior pituitary receives only 10-20% of its vascular supply from the superior and inferior hypophyseal arteries, with 80-90% derived from the hypophyseal venous portal circulation, thus making it susceptible to ischemia during hypotension [Stojanovic *et al*., 2008]. Pituitary tissue cannot regenerate, therefore ischemia induced necrosis will culminate in hypopituitarism [Stojanovic *et al*., 2008]. Such cases present more insidiously, as in our subject who presented with gradual onset of panhypopituitarism over 5-6 years, echoing classical Sheehan's syndrome which similarly results from severe hypotension (caused by peripartum hemorrhage), resulting in ischemia and necrosis of a normal but enlarged pituitary gland. Sheehan's syndrome typically evolves slowly and is often diagnosed many years after the index delivery. However, failure to lactate and amenorrhoea post-partum are classic early symptoms of Sheehan's, echoing our subject's presentation with amenorrhoea immediately post-DSS [Kelestimur, 2003]. Other situation where hypotension-induced hypopituitarism in normal non-adenomatous pituitary gland includes intra-operative cardiopulmonary bypass due to loss of pulsatile blood flow, predisposing subjects to pituitary ischemia [Mattke *et al*., 2002].

A 3rd possibility is that the dengue virus has neurotropic characteristics and a direct cytopathic effect on neural tissue. There are reports of atypical dengue manifestations of encephalitis and optic neuropathy where dengue virus antigens have been identified upon autopsy in central nervous system biopsies and the dengue virus itself has been observed in cerebrospinal fluid [Gulati & Maheswari, 2007]. This mechanism has been proposed to explain the well-known sequelae of hypopituitarism post-Hanta virus infection [Stojanovic *et al*., 2008].

It is possible that severe dengue, just as has been documented with Hanta virus, is also associated with hypopituitarism, secondary to the mechanisms outlined above – an issue that has yet to be systematically explored. The entity of hypopituitarism after hemorrhagic fever with renal syndrome (HFRS, secondary to Hanta virus transmitted by rodent vectors) were well-delineated in the literature [Stojanovic *et al*., 2008]. HFRS is a severe systemic infection associated with acute shock, vascular leakage and hypotension (as in DHF), in addition to acute renal failure which is not a feature of DHF [Stojanovic *et al*., 2008]. Post-mortem analyses revealed anterior pituitary hemorrhage and necrosis in 50-100% of fatalities [Stojanovic *et al*., 2008]. Direct viral invasion was confirmed in both endocrine and endothelial cells of the pituitary gland. Retrospective studies demonstrated that 18% of 60 HFRS survivors had evidence of at least one hormonal deficiency, with the most common deficiencies being growth hormone,

gonadotroph, corticotroph and thyrotroph abnormalities in that order. MRI evidence of pituitary atrophy and ESS was seen in 4 out of 5 patients with multiple hormonal deficiencies [Stojanovic *et al.*, 2008]. Time from the acute hemorrhagic fever to diagnosis of hypopituitarism in this cohort ranged from 0.5-11 years (median: 2 years) [Stojanovic *et al.*, 2008]. These clinical features and the natural history of hypopituitarism in HFRS survivors mimic those of Sheehan's syndrome just as in our subject. Patients often go undetected as symptoms (tiredness, weakness, decreased muscular strength, apathy, cold intolerance, and weight gain) are non-specific and can be attributed to post-viral symptoms. It is postulated that hypopituitarism in these cases may be secondary to: 1) hemorrhage (thrombocytopenia/increased microvascular permeability); 2) ischemia secondary to hypovolemia; 3) direct cytopathic effect of Hanta virus [Stojanovic *et al.*, 2008].

The World Health Organization (WHO) requires presence of both plasma leakage and circulatory failure to diagnose DSS [WHO, 2011]. Our subject had classical features of DSS: plasma leakage (hemoconcentration, pleural effusion), hypotension, reflex tachycardia and weak pulses. Although dengue IgM was negative in our subject, one should be aware that dengue IgM is detected in only 55% of patients with primary dengue infection between day 5-7 of illness [Schilling *et al.*, 2004]. It only becomes positive in all patients after day 7 [Schilling *et al.*, 2004]. Therefore, a negative dengue IgM on day 4 of illness did not exclude dengue infection in our subject. Dengue NS1 antigen, an earlier and more sensitive diagnostic indicator [Kumarasamy *et al.*, 2007], was not sent as it was not routinely available 6 years ago. Nevertheless the classical clinical features and a positive dengue IgG in our subject corroborate the diagnosis of DSS.

Lastly, it should be acknowledged that as there is no objective biochemical and imaging evidence of normal pituitary function/anatomy prior to our subject's hospitalization for DSS. It is possible our subject had idiopathic ESS preceding the DSS. However, the strong temporal relationship between onset of amenorrhoea (a clear marker of female hypogonadism) and DSS leads us to believe otherwise. Recognition of this relationship serves as a good teaching vignette to all clinicians treating dengue.

CONCLUSION

We have reported a rare case of panhypopituitarism in a DSS survivor. Recognition of the relationship between pituitary dysfunction and severe dengue can create huge impact in the post-dengue management, especially in dengue-endemic regions. Hypothesized mechanisms in this subject include pituitary infarction secondary to hypotension, or a direct cytopathic effect of the dengue virus. Subclinical PA secondary to asymptomatic pituitary hemorrhage however cannot be excluded. Physicians treating patients with severe dengue should be made aware of uncommon complications such as PA and the chronic sequelae of hypopituitarism. Future research is required to determine the need for and timing of pituitary axis assessment among DSS survivors.

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