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# Case study

# Transient hypothyroidism associated with viral Human Parechovirus encephalitis in a newborn



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# ABSTRACT

Human Parechovirus type 3 (HPeV-3) is a neurotropic virus which can cause neonatal encephalitis, presenting as encephalopathy with seizures and diffuse white matter lesions on brain imaging. Neurodevelopmental outcome is linked to the extent of white matter abnormalities. We report on a neonate with clinical and biochemical findings of transient central hypothyroidism associated with HPeV-3 encephalitis. The co-occurrence of transient hypothyroidism and viral encephalitis has not been reported in newborns before. Transient suppression of the hypothalamo-pituitary-thyroidal axis is described in critically ill babies as the nonthyroidal-illness syndrome. Assessment of thyroid function in neonatal cases of HPeV-3 infection is required to conclude whether a transient hypothyroidism as in nonthyroidal-illness syndrome may be triggered by viral meningoencephalitis and if treatment may influence neurodevelopmental outcome.

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#### 1. Introduction

Neonatal encephalopathy associated with seizures is a heterogeneous clinical entity, which can result from a variety of conditions. It is mostly associated with an acute

hypoxic-ischemic insult. However, perinatal stroke or haemorrhage, central nervous system (CNS) infections and metabolic disorders may all induce central nervous system dysfunction causing seizures. These conditions must be ruled out when clinical history, examination and biochemical findings are not consistent. CNS infection is the underlying

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etiology in 5–10% of neonates presenting with acute symptomatic seizures and encephalopathy.<sup>1–4</sup> Although CNS infection commonly involves (bacterial) meningitis, viral meningo-encephalitis constitutes a considerable cause of neonatal CNS infection in one out of four.<sup>4</sup>

Enterovirus (EV) and Herpes Simplex Virus (HSV) are the best known causes of viral meningo-encephalitis and associated neonatal seizures. However, as described by Verboon-Maciolek et al.<sup>5</sup> Human Parechovirus (HPeV) encephalitis should also be investigated in an atypical presentation of neonatal seizures. HPeV is a neurotropic virus, clinical undistinguishable of EV. HPeV can lead to severe encephalitis with associated typical white matter lesions on cranial ultrasound and brain MRI, whereas Herpes Simplex Virus encephalitis and Enterovirus encephalitis manifest diffuse grey and white matter changes<sup>5,6</sup>. HPeV has been reclassified in the new genus Parechovirus in the family of the Picornaviridae. HPeV cannot be detected by standard EV PCR because of the genetic differences between both viruses. The diagnosis of HPeV infection can be made from a positive HPeV PCR in CSF or blood, but can easily be overlooked as HPeV PCR is not yet a standard examination in most centers.

In this case report, we describe a neonate with clinical symptoms and biochemical findings of transient central hypothyroidism, presenting with acute symptomatic seizures, encephalopathy and diffuse white matter abnormalities on brain MRI, triggered by HPeV type 3 encephalitis.

# 2. Case study

This girl was born full term by an uncomplicated vaginal delivery. Pregnancy had been uneventful. She was the second child of healthy, non-consanguineous parents. Birth weight, length and head circumference were at the 25th centile. She was discharged on day 4. She was referred on day 9, featuring a sepsis-like illness with irritability, poor feeding and seizures. She presented without a fever or rash. On clinical examination by referral, she had a large tongue and a hoarse voice. She developed a progressive encephalopathy with apnea and clonic movements. Electro-encephalographic (EEG) monitoring showed repetitive, multifocal seizures on an abnormal, discontinuous background. Convulsions were treated successfully by antiepileptic drugs (first: Phenobarbital 40 mg/kg and add-on Levetiracetam 40 mg/kg). Cranial ultrasonography performed on admission and during the first month showed extensive periventricular echogenicity. Brain MRI on day 9 showed areas of restricted diffusion in the periventricular white matter, corpus callosum, deep white matter, optic radiation, internal capsule and both thalami (Fig. 1).

#### 2.1. Laboratory findings

The routine laboratory test and CSF examination were all normal. Thyroid function test disclosed a decreased free T4 0.80 ng/dl (ref. range 0.93–1.70 ng/dl), a decreased T3 55 ng/dl (ref. range 80–200 ng/dl) and low thyroid-stimulating hormone 0.18 mIU/l (ref. range 0.27–4.20 mIU/l). Initial neonatal screening on day 4 for primary congenital hypothyroidism provided a normal test result for TSH (TSH level of 1.6 mIU/l;

cut-off level of 15 mIU/l). Maternal medical history was negative with respect to thyroid problems. Blood tests for maternal thyroid antibodies (Thyroid peroxidase antibodies, TSH-receptor antibodies) were negative. Further imaging showed a normal anatomical position and size of the thyroid gland and a normal aspect of the pituitary gland on brain MRI. Hypothalamic—pituitary function tests initially showed low IGF-1 levels, with normalization after one week, other signs of congenital hypopituitarism were lacking. Thyrotropin releasing hormone stimulation test and metabolic screening tests were normal. Based on clinical and laboratory findings, hypothyroidism was diagnosed and treated with L-Thyroxin from day 10 (15  $\mu$ g/kg).

#### 2.2. Microbial test

Cerebrospinal fluid (CSF) analysis did not reveal pleocytosis or aberrant glucose or protein levels. CSF gram staining, culture and viral tests including EV PCR and HSV PCR were negative. Because of the unusual presentation of an encephalopathy with severe white matter abnormalities, targeted HPeV PCR analysis on stored CSF was requested after expert advice. HPeV type 3 was identified on real-time PCR.

#### 2.3. Treatment and follow-up

Thyroxine replacement therapy was paralleled by the successful treatment of convulsions. The encephalopathy resolved during the following days, other clinical symptoms assigned to hypothyroidism improved more sustained. Brain MRI on day 16 revealed persistent white matter abnormalities. An electro-encephalogram on day 15 showed an improvement of the background activity but persistent multifocal epileptic discharges.

Thyroxin treatment was tampered and successfully stopped after one month of treatment, with normalization of the thyroid function test, suggesting a transient hypothyroidism. Cranial ultrasound at the age of two months showed decreased white matter abnormalities and no evolution to cystic lesions. The neurodevelopment outcome at four months was still favorable. Brain MRI showed normalization of the white matter on the diffusion-weighted images. No cystic lesions were present. Further follow-up was planned (Fig. 2).

# 3. Discussion

We report on a neonate with transient hypothyroidism and viral encephalitis by HPeV type 3. Both conditions may independently induce neonatal encephalopathy. In this case, the clinical presentation of viral encephalitis was blurred due to absence of fever and because of absence of pleocytosis in the cerebrospinal fluid. Clinical symptoms of congenital hypothyroidism, arising either from primary thyroid dysfunction or from central pituitary dysregulation (secondary or central hypothyroidism), are initially subtle and nonspecific at birth. The most common symptoms at diagnosis are lethargy, feeding difficulties, prolonged jaundice, umbilical hernia and constipation.<sup>7–9</sup> Grant et al. described 38 infants who had been suspected of having congenital hypothyroidism on

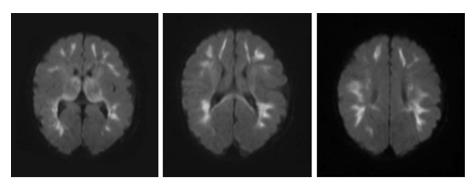


Fig. 1 – Magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) at day 9 showed the distinctive pattern of white matter involvement: areas of restricted diffusion in the periventricular white matter, corpus callosum, deep white matter, optic radiation, internal capsule and both thalami.

clinical grounds before the screening result was known. There was a significantly increased incidence of persistence jaundice, feeding difficulties, lethargy, macroglossia, umbilical hernia, constipation and cold or mottled skin.<sup>8</sup> Alm et al. found similar findings.<sup>10</sup> Virtanen et al. compared the clinical symptoms at the age of 6 days in hypothyroid newborns with those in infants with false positive screening test results. Icterus, large tongue, abdominal distension, umbilical hernia, hypothyroid appearance and cold skin were more prevalent in the hypothyroid group.<sup>11</sup> Nevertheless, even infants with severe hypothyroidism, diagnosed through newborn screening, can be asymptomatic at the time of diagnosis.<sup>8,10</sup> The lack of distinctive clinical symptoms, coupled with the importance of early treatment, has led to the implementation of routine neonatal screening.<sup>7,12,13</sup> In our center, newborn screening for hypothyroidism is based on a primary TSH-test (cut-off level of 15 mIU/l). Only infants with primary congenital hypothyroidism and thus an elevated serum TSH, will be detected.<sup>12,13</sup> However, variants of congenital hypothyroidism that are characterized by an inappropriate low TSH level, such as central (hypopituitary) and preterm congenital hypothyroidism, will be missed with TSH-based screening test and requires free T4 (fT4) measurement.<sup>7,11</sup> Therefore clinical recognition of congenital hypothyroidism is still very important. Extra attention is warranted in a selected group of newborns: neonates with congenital malformations, premature neonates, neonates born to a mother with thyroidal illness and critically ill newborns. Transient central hypothyroidism with low fT4 and low or normal TSH is described in

critically ill babies after the use of specific drugs (steroids, dopamine) or due to the effect of uncontrolled maternal hyperthyroidism (Graves' disease). The combination of a depressed thyroid function (isolated hypothyroxinemia with low fT4, low or normal TSH and normal response to TRH test) and neonatal sepsis has been described as the nonthyroidal-illness syndrome (NTIS) or euthyroid sick syndrome in bacterial sepsis or septic shock.<sup>14,15</sup> These entities arise from acute suppression of the hypothalamo–pituitary–thyroidal axis.<sup>14–16</sup> In NTIS, this is triggered by an inflammatory mechanism. Depressed thyroid levels are significantly correlated with disease severity and mortality in those cases.<sup>14,16</sup>

The current patient featured an umbilical hernia, a large tongue and an abnormal cry at day 10. These symptoms are uncommon in patients with neonatal encephalopathy, and urged us to re-test the patient's thyroid function. Initial neonatal screening for primary congenital hypothyroidism provided a normal test result for TSH. Secondary (central) hypothyroidism as well as maternal thyroid problems were excluded, based on a normal TRH test and on the absence of maternal antibodies, respectively. Although helpful in the diagnosis of NTIS, reverse T3 hasn't been measured in our patient. Reverse T3 will rise promptly during the acute phase of critical illness. However, difference in plasma hormone concentrations between the acute and the prolonged phase of critical illness, as well as changes in relation to feeding and fasting conditions, should be considered when evaluating thyroid function in NTIS.<sup>16</sup>

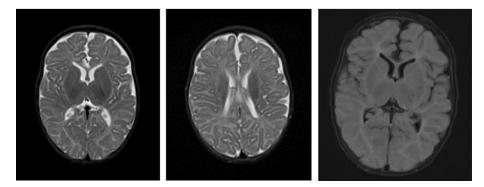


Fig. 2 – Magnetic resonance imaging (MRI) T2-weighted spin-echo sequences (left) and fluid-attenuated inversion recovery sequence (right) at 4 months of age. No cystic lesions or ventricular dilatation.

HPeV type 3: Cases in literature	MRI	Neurodevelopmental outcome
Verboon-Maciolek et al., 2008	10 cases: ranging from extensive cystic white matter damage to mild punctate white matter lesions	<ul> <li>Long term outcome at 2–5 years of age:</li> <li>Favorable in 5 patients</li> <li>Cognitive problems in 2 patients (learning and concentration difficulties)</li> <li>Unfavorable in 3 patients: 1 CP plus severe delay and epilepsy, 1 mild distal hypertonia and learning difficulties and 1 with mild hemiplegia.</li> </ul>
Van Zwol et al., 2009 Gupta S. et al., 2010	2 cases: 1 extensive white matter abnormalities 1 case: extensive white matter abnormalities	Fatal outcome in both cases Abnormal at 6 months of age
Renna S. et al., 2014	1 case: mild white matter abnormalities	Favorable at 15 months of age
Belcastro et al., 2014	1 case: extensive white matter abnormalities	Abnormal at 4 months of age

Table 1 – Overview of Magnetic Resonance Imaging Results and Neurodevelopmental Outcome of 15 Patients with Human Parechovirus Encephalitis reported in the literature.

Recently, a case of congenital hypothyroidism with comparable diffuse white matter abnormalities on diffusion imaging was reported.<sup>17</sup> However, the association between diffuse white matter lesions and congenital hypothyroidism is not further supported in the literature. Older studies found no differences in conventional brain MRI (T1/T2) imaging between neonates with congenital hypothyroidism prior to treatment and MRI findings of normal neonates.<sup>18</sup> Therefore, we presume that the MRI findings in our case could not be explained by hypothyroidism. Moreover, the extensive white matter abnormalities on brain MRI are suggestive for neonatal HPeV type 3 encephalitis. Whereas other viral aggressors like HSV encephalitis typically exhibit the combination of diffuse grey and white matter changes, HPeV type 3 has a predilection for the white matter premyelinating oligodendrocyte, resulting in disturbed axonal development and neuronal apoptosis.<sup>5,19</sup> Without brain imaging by cranial ultrasound or MRI, HPeV encephalitis may be easily missed, as routine cerebrospinal fluid examination is normal in the majority of cases with enteroviral and HPeV infection. Moreover, HPeV is not detected with standard EV PCR. Hence, HPeV PCR should be assessed in an atypical presentation of neonatal seizures with diffuse white matter abnormalities on cranial ultrasound or brain MRI.

Neurodevelopmental outcome after neonatal HPeV encephalitis correlates with the severity of MRI imaging abnormalities.<sup>5,19</sup> Verboon-Maciolek et al.<sup>5</sup> described 10 cases of neonatal encephalitis due to HPeV-3. In eight cases diffusion weighted images were present and outcome correlated with the severity of white matter injury on MRI. Similarly, an abnormal developmental outcome was reported in two cases with major white matter lesions,<sup>19,20</sup> whereas a more favorable outcome was noted in one neonate after HPeV-3 infection with less extensive white matter injury and absence of neonatal seizures.<sup>21</sup> Van Zwol et al.<sup>22</sup> reported two fatal cases of HPeV encephalitis, however, only one had extensive white matter abnormalities on MRI (Table 1).

#### 4. Conclusion

To the best of our knowledge, this is the first case of viral encephalitis associated transient hypothyroidism in a newborn. Neonatal HPeV type 3 encephalitis is a rare cause of neonatal encephalopathy with seizures and extensive white matter abnormalities on diffusion-weighted imaging on brain MRI. Neonatal encephalopathy and neonatal seizures require comprehensive diagnostic measures, comprising longitudinal neurophysiological monitoring, brain imaging, preferably by means of MRI, a metabolic blood screen, and a full CSF examination, with CSF culture and extensive viral tests, including HPeV PCR. This case highlights the assessment of thyroid function test in critically ill neonates. Systematic evaluation of thyroid function in neonatal cases of HPeV-3 infection is required to conclude whether a transient hypothyroidism as in NTIS may be triggered by viral meningoencephalitis and if treatment may influence neurodevelopmental outcome.

# **Conflict of interest**

None.

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