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Multiple Cerebral Hemorrhages and White Matter Lesions Developing after Severe hMPV Pneumonia in a Patient with Trisomy 13: A Case Report and Review of the Literature

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Human metapneumovirus (hMPV) is a common cause of upper and lower respiratory tract infections in children. A few case reports have described hMPV encephalitis or encephalopathy. Neuroimaging data on patients with hMPV encephalitis are scarce. We report a patient with trisomy 13 who developed severe hMPV pneumonia, multifocal cerebral and cerebellar hemorrhagic infarctions and extensive cerebral white matter demyelination. Although adult respiratory distress syndrome and disseminated intravascular coagulation contributed to the devastating central nervous system (CNS) lesions, endothelial dysfunction of the CNS caused by hMPV infection probably also played a pathophysiological role in this case.

Keywords: adult respiratory distress syndrome; encephalitis; hemorrhagic infarction; human metapneumovirus; trisomy 13
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Introduction

Human metapneumovirus (hMPV) is a common cause of upper and lower respiratory tract infections in children. Few case reports have described hMPV encephalitis or encephalopathy (Schildgen et al. 2005; Kaida et al. 2006; Hata et al. 2007; Arnold et al. 2009; Sanchez Fernandez et al. 2012; Yokota and Enoki 2013; Niizuma et al. 2014; Webster et al. 2014; Fok et al. 2015; Vehapoglu et al. 2015; Jeannet et al. 2017; Tan and Wee 2017). Here, we report a patient with trisomy 13 who experienced severe hMPV pneumonia, associated with profound central nervous system (CNS) complications. The neuroimaging findings suggest CNS involvement associated with a severe hMPV infection.

Case Presentation

The patient was a 6-year-old girl born spontaneously after 38 weeks of gestation to healthy, non-consanguineous Japanese parents. She was diagnosed with trisomy 13 (full trisomy) at 3 months of age after examination of external malformations. Her early development was severely delayed; she lacked head and roll control and could not self-sit. At the age of 6 years, she was bedridden and required nasogastric tube nutrition. She could not enunciate meaningful words but her facial expressions in response to her surroundings were rich when she was brought to our hospital with a high fever, dyspnea, and low oxygenation status. Immunochromatography of a nasal swab was positive for hMPV but negative for adenovirus and influenza A/B virus. A chest X-ray revealed reduced permeability in the left lower lung field. She was admitted under a diagnosis of hMPV pneumonia. On hospital day 6, her oxygenation status deteriorated and chest X-ray revealed worsening adult respiratory distress syndrome (ARDS) (Fig. 1). Tracheal intubation and ventilator management were started in the intensive care unit but the hypoxemia persisted. On hospital day 10, bloody tracheal aspiration was observed, indicating the development of disseminated intravascular coagulation (DIC). After a few weeks of intensive treatment, she recovered somewhat and was successfully extubated on hospital day 36. Rehabilitation started but she lacked spontaneous movements of the extremities. On hospital day 45, brain MRI revealed multiple high-intensity

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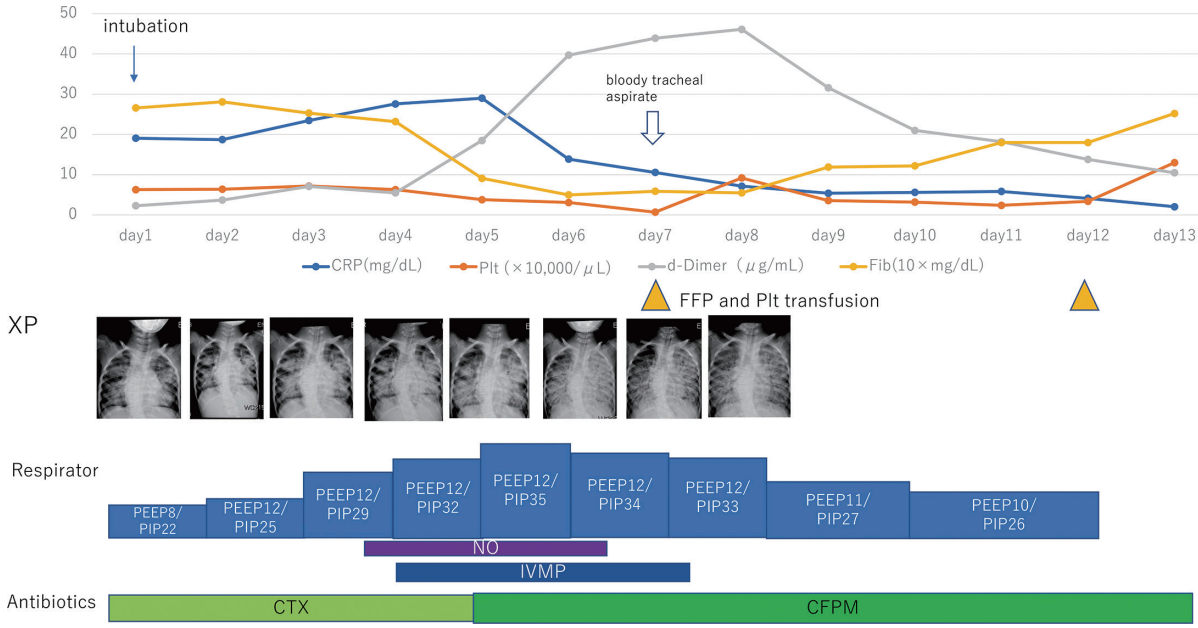

Fig. 1. The early clinical and treatment course of the patient in the intensive care unit.
XP, X-ray photograph; FFP, fresh frozen plasma; FFP, fresh frozen plasma; Plt, platelet; Fib, fibrinogen; PEEP, positive endo-expiratory pressure; PIP, peak inspiratory pressure; NO, inhalation of nitric oxide; IVMP, intravenous methylprednisolone therapy; CTX, cefotaxime; CFPM, cefepime.

T1-weighted image (T1WI) signals, high- and low-intensity T2-weighted image (T2WI) (Fig. 2A-C) and fluid-attenuated inversion recovery (FLAIR) signals (Fig. 2D-F), and low-intensity T2* signals (Fig. 2G-I) in both posterior limbs, the internal capsule, the thalamus and basal ganglia, and the subcortical white matter of the right and left cerebral hemispheres. Low-intensity T2* lesions were also evident in the corpus callosum, brain stem, and cerebellum (data not shown). These findings indicated that hemorrhagic infarctions had developed several weeks prior. Furthermore, FLAIR (Fig. 2D-F), but not diffusion-weighted imaging (DWI) (Fig. 2J-L), revealed an extensive high-signal area in the deep cerebral white matter, suggestive of a demyelinating white matter lesion. Spinal MRI was unremarkable. She was discharged after completion of inpatient rehabilitation and is being followed up regularly as before. Her family provided informed consent for publication of this case report.

Discussion

hMPV encephalitis was first reported by Schildgen et al. (2005) who detected hMPV RNA in postmortem lung and brain tissues, suggesting that direct viral invasion of the brain caused hMPV encephalitis. Other case reports of patients with hMPV encephalitis revealed positive respiratory system samples on viral PCR (Kaida et al. 2006; Hata et al. 2007; Arnold et al. 2009; Yokota and Enoki 2013; Niizuma et al. 2014; Webster et al. 2014; Fok et al. 2015; Vehapoglu et al. 2015), but hMPV RNA in cerebrospinal fluid was detected in only three cases (Sanchez Fernandez et al. 2012; Jeannet et al. 2017; Tan and Wee 2017). Table 1 summarizes the clinical, virological and neuroimaging findings of previously reported cases and the present case. Of a total of 18 patients, 13 developed seizures or disturbed consciousness after presenting with respiratory symptoms. Four patients exhibited sudden-onset status epilepticus or disturbed consciousness. Increases in the cerebrospinal fluid white blood cell count were detected in only 5 of 14 patients examined. These findings imply that an encephalopathic pathomechanism (such as a cytokine storm) develops in some of these patients (Hata et al. 2007; Yokota and Enoki 2013; Niizuma et al. 2014). The patient was under intensive care management with sedatives, which rendered it difficult to evaluate the acute neurological symptoms. Furthermore, we cannot conclusively state that hMPV encephalitis was a relevant factor, as we did not subject a cerebrospinal fluid or cerebral tissue sample to viral PCR. However, we believe that the immunochromatographic data derived from the nasal swab are reliable.

Neuroimaging data for patients with hMPV encephalitis are scarce (Schildgen et al. 2005; Arnold et al. 2009; Sanchez Fernandez et al. 2012; Fok et al. 2015; Tan and Wee 2017). Previous reports described multifocal subcortical white matter high-signal lesions on T2WI and FLAIR (Schildgen et al. 2005; Arnold et al. 2009; Fok et al. 2015; Tan and Wee 2017), and high-intensity cortical and white matter lesions on FLAIR, T2WI, and DWI (Sanchez Fernandez et al. 2012). It may be that multiple subcortical white matter lesions are characteristic of hMPV encephalitis. However, some cases exhibited no neuroimaging abnormalities, suggesting the potential for better outcomes. All four patients with normal MRI findings remain alive

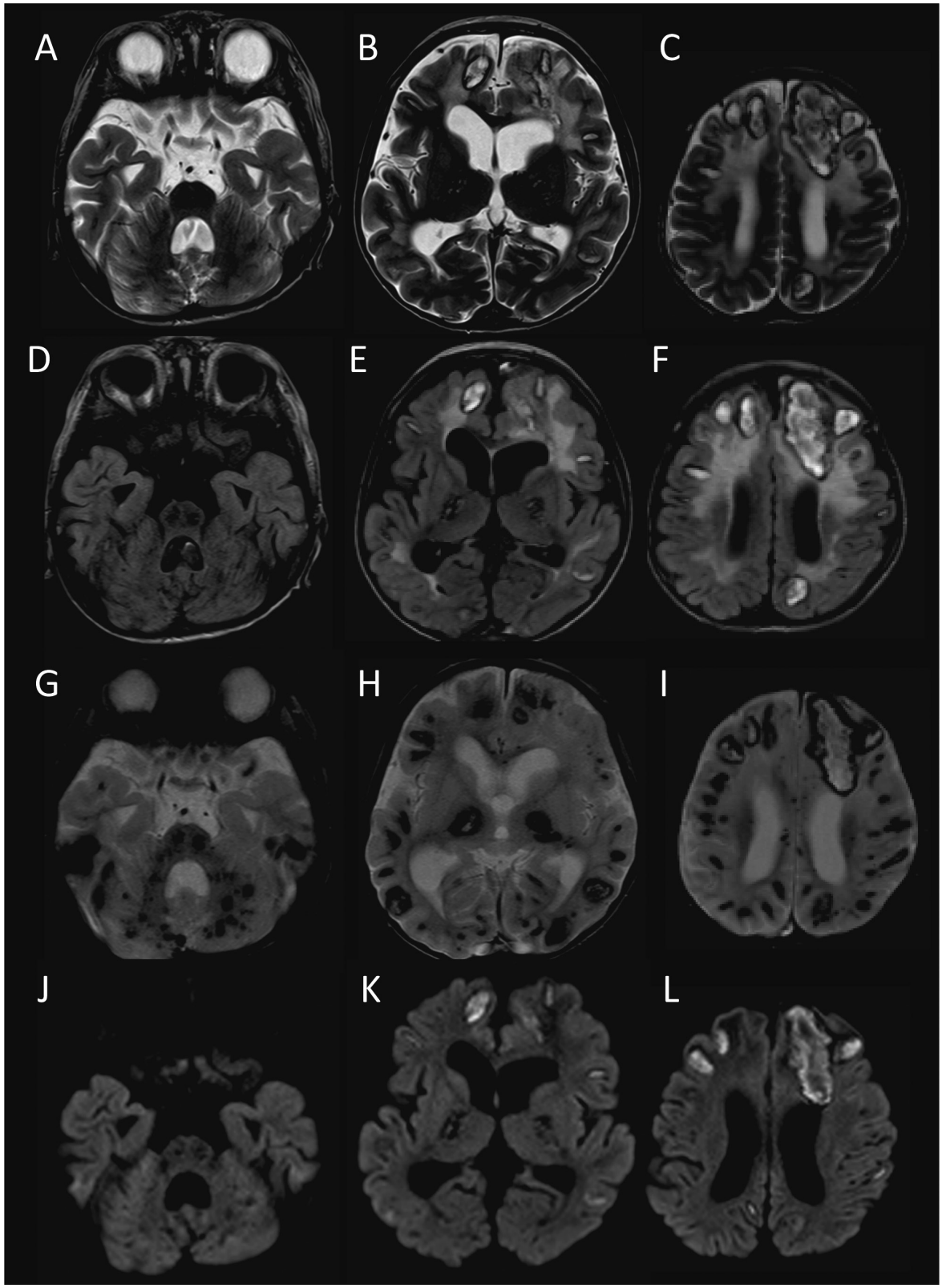

Fig. 2. MRI findings.
(A-C) T2 weighted image (T2WI); (D-F) Fluid-attenuated inversion recovery (FLAIR); (G-I) low-intensity T2*; (J-L) diffusion weighted image (DWI) on day 45 of admission. Multifocal hemorrhagic lesions are evident in the cerebral subcortical white matter, bilateral thalamus, basal ganglia, posterior limbs of the internal capsule, pons and cerebellum. These findings presented as low-intensity T2* signals, and both low- and high-intensity signals on T2WI and FLAIR. The T2WI and FLAIR images also exhibited an extensive high-intensity lesions in the front-parietal white matter, suggestive of demyelination. DWI showed no corresponding high signal white matter lesions as T2WI and FLAIR.

Table 1. Clinical and neuroimaging summary of previously reported hMPV encephalitis/encephalopathy cases and the present case.

References	Age/Sex	Seizure	Respiratory infection symptoms	Increase in CSF-WBC	RT-PCR of CSF	RT-PCR of respitratory system	RT-PCR of postmortum brain tissue	Immuno-chromatography of hMPV	Outcome	Brain MRI findings
Schildgen et al. (2005)	1.2/M	Yes	No	No	−	NM	+		Died	multiple cortical and subcortical FLAIR high signal lesions.
Kaida et al. (2006)	1 /F	NM	NM	NM	NM	+			NM	NM
Hata et al. (2007)	0.5/F	Yes	Yes	NM	−	+			Died	low dencity areas in the WM (CT scan)
Arnold et al. (2009)	3/F	Yes	Yes	Yes	−	+			Died	cerebral edema
Arnold et al. (2009)	5/F	Yes	Yes	No	−	+			NM	NM
Arnold et al. (2009)	4/F	No	Yes	Yes	−	+			NM	multiple hyperintensity lesions in WM
Arnold et al. (2009)	3/F	No	No	No	−	+			NM	NM
Arnold et al. (2009)	4/M	Yes	Yes	NM	−	+			NM	NM
Sanchez Fernandez et al. (2012)	10/F	Yes	No	Yes	+	+			Alive (attention and executive deficits)	1) multiple T2WI, FLAIR, DWI hyperintense lesions (subcortical, deep WM, external capsle), 2) multifocal cortical thickening with high T2WI and DWI signal and later atrophy
Yokota and Enoki (2013)	2/M	No	No	No	−	+			Alive (No sequelae)	unremarkable
Niizuma et al. (2014)	3.5/F	Yes	Yes	No	−	+			Alive (No sequelae)	unremarkable
Webster et al. (2014)	1.3/F	Yes	Yes	No	NM	+			Alive (No sequelae)	NM
Webster et al. (2014)	1.5/F	Yes	Yes	No	NM	+			Alive (No sequelae)	unremarkable
Fok et al. (2015)	47/M	No	Yes	No	−	+			Alive (No sequelae)	multiple small legions with FLAIR and DWI hyperintensities in bilateral subcortical white matter and external capsule, with perirolandic predominance
Vehapoglu et al. (2015)	0.3/M	Yes	Yes	Yes	−	+			Alive	unremarkable
Jeannet et al. (2017)	61/M	Yes	Yes	Yes	+	+			NM	NM
Tan and Wee (2017)	32/M	No	Yes	No	+	+			Alive (Sequelae+)	multiple T2WI and FLAIR high signal lesions
Index case	6/F	No	Yes	ND	ND	ND		+	Alive	1) multiple subcortical WM bleeding, 2) thalamus, basal ganglia, pons and cerebellum bleeding, 3) hyperintensity on FLAIR in the WM

F, female; M, male; NM, not mentioned; ND, not done; CSF-WBC, cerebrospinal fluid white blood cells; WM, white matter; +, positive; −, negative.

and three recovered without sequelae (Yokota and Enoki 2013; Niizuma et al. 2014; Webster et al. 2014). No prior report has described the extensive multiple CNS hemorrhages and cerebral white matter demyelination noted in the present patient. There is also no previous report on hemorrhagic brain infarction associated with trisomy 13.

In our case, multiple factors may have combined to cause the development of cerebral hemorrhagic infarction including cerebral venous congestion (caused by the increased intrathoracic pressure associated with high-pressure ventilation), hypoxemia, and DIC. In terms of DIC neuroimaging, some reports have described cerebral infarctions accompanied by septic DIC, which is caused by arterial embolisms (Kako et al. 2021). Our present case exhibited intracranial hemorrhage similar to that seen in some coronavirus disease 2019 (COVID-19)-associated infections that were accompanied by devastating lung disease. The many risk factors included therapeutic anticoagulation, extracorporeal membrane oxygenation (ECMO), mechanical ventilation to treat the ARDS, and DIC (Daly et al. 2021). COVID-19 infects vascular endothelial cells after binding to vascular angiotensin-converting enzyme 2 (ACE2) (Six et al. 2022), triggering DIC and multiple organ failure (including ischemic stroke caused by embolisms) (Six et al. 2022). However, ischemic stroke after COVID-19 infection has been proposed to be multifactorial in nature, including the development of a cytokine storm, activation of the innate immune system, embolic events triggered by pre-existing or new-onset arrhythmias, hypoxia-induced ischemia secondary to severe pulmonary disease, thrombotic microangiopathy, and direct infection of the brain endothelium that causes viral-induced vasculitis (Zakeri et al. 2021). Notably, a recent report found that hMPV could infect both microvascular endothelial cells and lung epithelial cells, and that these cells induced immune responses (Bugatti et al. 2020). hMPV can attach to many cell surface receptors before entering the cells; the viral receptors include heparan sulfate, arginine-glycine-aspartate (RGD)-binding integrins, and other protease-sensitive surface proteins (Cox and Williams 2013). A severe inflammatory response in the brain vascular endothelium may trigger cytokine dysregulation, increase vascular permeability, and induce extravasation of immune cells, resulting in capillary rupture and brain hemorrhage (Zakeri et al. 2021). Such processes may have played roles in our present patient. Neuroimages of COVID-19-infected patients with neurological symptoms revealed acute disseminated encephalomyelitis-like white matter demyelination (Paterson et al. 2020), which may also occur in patients with hMPV infections.

In conclusion, we report a patient with trisomy 13 who developed severe hMPV pneumonia, multifocal cerebral hemorrhagic infarctions and extensive white matter demyelination. Although ARDS and DIC contributed to the development of the devastating CNS lesions, endothelial dysfunction of the CNS caused by hMPV infection probably also played a pathophysiological role in the present case.

Conflict of Interest

The authors declare no conflict of interest.

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