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Case Report

Mild encephalopathy with reversible splenial lesion associated with echovirus 6 infection: a case report and review of the literature

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ABSTRACT

Background. Mild encephalopathy with reversible splenial lesion (MERS), a clinic-radiological syndrome distinguished by reversible encephalopathy onset, has been increasingly recognized in Caucasian children.

Case. We describe a MERS case in a previously healthy 4-year-old girl admitted to the hospital with abnormal consciousness level, muscle weakness, dysphagia and dysarthria after a 4-day history of diarrhea and fever. Magnetic resonance imaging (MRI) of the brain showed hyperintensity in the corpus callosum splenium. Electroencephalogram was normal and cerebrospinal fluid (CSF) culture negative. The stool sample was positive for Echovirus 6 and serology test confirmed the infection. The child's condition gradually improved and the MRI, after 15 days, depicted a normal brain. Only a mild speech impairment was persistent at discharge, which disappeared one month later. We performed a literature review about pediatric MERS cases demonstrating that infectious agents have been rarely isolated in CSF.

Conclusion. MERS has an overall good prognosis independently from the treatment approach; this is confirmed by our case - one of the first reported with an Echovirus 6-related encephalopathy.

Key words: mild encephalopathy with reversible splenial lesion (MERS), echovirus, encephalopathy, child.

Mild encephalopathy with reversible splenial lesion (MERS) is a disorder characterized by prodromal symptoms such as fever, cough, vomiting or diarrhea, followed by mild encephalopathy 1-7 days later with a documented reversible splenial lesion. Lesions are typically hyperintense in T2-weighted brain magnetic resonance imaging (MRI) and demonstrate a transiently homogeneous low apparent diffusion coefficient (ADC). Takanashi et al.[1] proposed to classify this encephalopathy in MERS type I, describing patients with an isolated splenium corpus callosum (SCC) lesion and in MERS type II for patients with extensive white matter and/or lesions involving the entire corpus callosum (CC). The most relevant and common neurological MERS symptoms, which tend to completely recover within 1 month, are behavioral changes, consciousness disturbance and seizures.[2-5]

Numerous infectious diseases are associated with MERS in children: rotavirus (RV),[6-14] cytomegalovirus (CMV),[15-17] influenza A and B,[5,16-28] parainfluenza,[29] mumps[2-30,31] as well as other viral agents such as adenovirus,[16] human herpesvirus-6 (HHV-6),[32] human herpesvirus-1,[17] parvovirus B19,[33] enterovirus (EV)[17] and Epstein-Barr virus (EBV).[34] Also bacterial infections have been described related to MERS cases, namely *Escherichia coli*,[28] *Enterococcus faecalis*,[35] *Salmonella*,[16] *Campylobacter jejuni*[28] and *Mycoplasma pneumoniae*.[17,28,36-44]

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Herein we describe a pediatric patient with Echovirus 6 infection and transient isolated SCC lesion on the brain MRI followed by extensive medical literature review about MERS in children.

Case Report

A previously healthy 4-year-old Caucasian girl with a 4-day-history of fever and diarrhea and mildl dehydration, was referred to our hospital in summer 2018. Patient's and family medical history was unremarkable. Physical examination on admission showed a body temperature of 38°C with a heart rate of 130 beats per minute, respiratory rate of 36 breaths per minute, oxygen saturation of 98% breathing room air and blood pressure of 103/64 mmHg. Chest and abdominal examination was normal. Neurological examination revealed an abnormal consciousness level, muscle weakness, dysphagia and dysarthria. The patient was responsive to painful stimuli with Glasgow Coma Scale score of 12 (eyes 3, verbal 4, motor 5), showed normal reflexes in the extremities; Kernig's and Babinski's signs were absent. Peripheral blood analysis showed a white blood cell count of 6970/μL, hemoglobin 10.6 g/dl, platelet count 325.000/μL and C-reactive protein 130 mg/L (normal value: <5). Biochemical parameters and blood gas analysis were normal. Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed 125 white cell/ml, increased protein 50 mg/dl and normal glucose 52 mg/dl. Isotonic fluids and empirical intravenous antibiotic treatment with ceftriaxone and intravenous acyclovir were started. Real Time-Polymerase Chain Reaction (RT-PCR) to detect CMV, EBV, EV, influenza viruses and herpes viruses in CSF were negative. Bacterial CSF cultures were also negative. Specific serum IgM antibodies (ELISA) against EBV, influenza virus, parainfluenza viruses, parvovirus B19, herpes viruses and CMV were negative. Conversely, serological tests for influenza A, adenovirus, HHV-6 and varicella demonstrated previous infections. RV detection test was negative. RT-PCR was also negative for influenza A and B in the pharyngeal swab. Urine analysis was normal. Electroencephalogram (EEG) revealed high-voltage slow waves on both temporal regions, with no paroxysmal discharge activity. Brain MRI, on day 2 of hospitalization, showed a focal high-signal lesion of SCC on T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted images (Fig. 1). Specific serum IgM and IgA antibodies (ELISA) against Echovirus were positive and the stool culture confirmed an acute infection with Echovirus 6. We interrupted ceftriaxone and acyclovir therapy on day 5. In consideration of persistent neurological symptoms such as muscle weakness, dysphagia and dysarthria combined with drowsiness and ataxia, brain MRI results, we initiated intravenous methylprednisolone treatment (2 mg/kg/day) for 5 days and continued the treatment with prednisone per os (2 mg/kg/day) for 2 weeks and subsequent decalage. A progressive clinical improvement was already noted on day 7 of hospitalization and continued until neurological symptoms disappeared, when the girl turned to a normal consciousness level and restarted drinking fluids. Fifteen days after admission, follow-up brain MRI and EEG were normal. The patient was discharged without neurological sequelae, except for a residual speech impairment, which had disappeared at her one-month follow-up visit. Informed consent was obtained by the parents for all procedures and for the publication of this case.

Discussion

EV epidemic outbreaks occur in summer or early fall in temperate regions. Echovirus 6 is one of the most frequently detected EV worldwide.[45] EVs are classified in 4 species: (a) human enterovirus A (coxsackie virus A2-A8, A10, A12, A14, and A16; EV71, 76, 89, 90, and 91), (b) human enterovirus B (coxsackie virus A9 and CVB1-CVB6; echovirus 1-7, 9, 11-27, and 29-33; EV69, 73-75, 77-88, 97, 100, and 101), (c) human enterovirus C (coxsackie virus A1, A11, A13, A17, A19-A22, and A24; polioviruses 1-3;

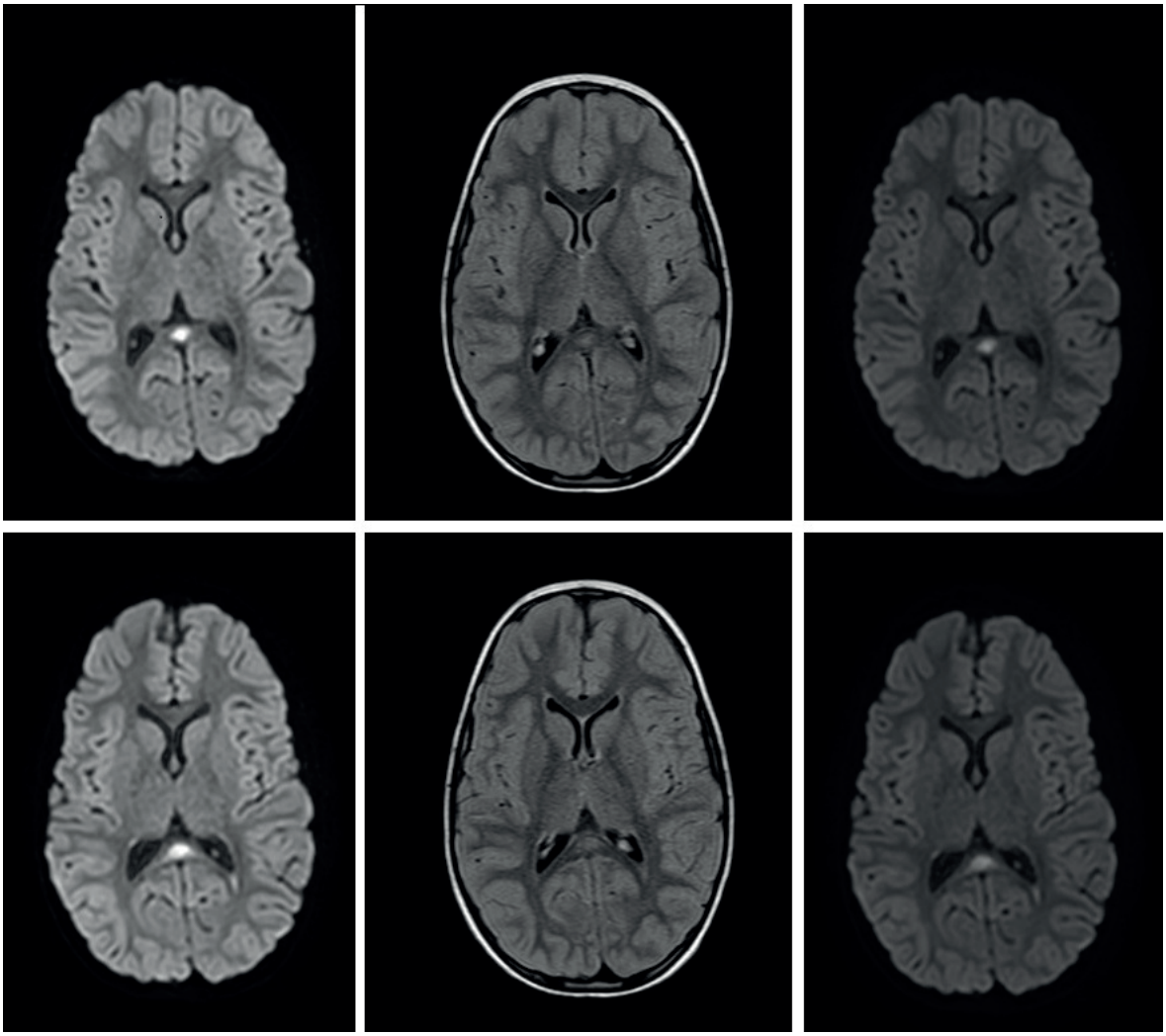

Fig. 1. MRI imagines on day 2 with hyperintensity in the SCC.

EV96), and (d) human enterovirus D (EV68 and EV70).[46] Echovirus (E) is the major causative agent of aseptic meningitis, and E6, E9, E11, E13, E19, E30 are the most common EV types detected in patients with aseptic meningitis. Consciousness disturbance, ataxia, acute muscle weakness, dysarthria and dysphagia, as reported in our patient, are typical neurological symptoms of EV-related encephalitis. Skin rashes and diarrhea are common non-neurological symptoms in EV infections.[45]

Brain MRI, in the presented case, revealed a transient splenial lesion, based on which we diagnosed MERS, a benign disorder characterized by homogenously reduced diffusion lesions (type I MERS), occasionally associated with extensive white matter and/or entire callosal lesions (type II MERS) on brain MRI.[1,2,47] Kobata et al.[6] eported for the first time a RV-related MERS case. In 2004, Tada et al.[2] described MERS as a new encephalopathy with a mild clinical course and good outcome.

We performed a literature review on pediatric MERS cases until July 2018 using Pubmed and Google database for English, Italian and Japanese language publications to clarify clinical features, etiology, neuroimaging and prognosis of this condition. The search was performed using the following keywords: ”enterovirus”, “echovirus”, “encephalitis”, ”encephalopathy”,

"mild encephalitis/encephalopathy with a reversible splenial lesion", "MERS" and "pediatric MERS". We identified 165 cases, including 52 English-language full reports (145 cases), 1 Japanese-language full report (1 case)[48] and 9 English-language abstracts (11 cases). Inclusion criteria were age less than 18 years and encephalopathy by means of brain MRI showing reversible hyperintensity of the splenium of the corpus callosum.

In the 165 pediatric MERS cases, mean age at time of diagnosis was 5.04 years (range 1 day-18 years) and male/female ratio (88/77) was 1.14. Clinical characteristics, laboratory data, neuroimaging results, and patient outcomes are summarized in Table I.

Considering the demographic distribution of patients, MERS occurs mostly in South East Asia, with 84 Japanese cases, 53 Chinese, 9 Australian and 9 Turkish cases, 3 Belgium cases, 1 case from Switzerland, United Kingdom, Poland, Malaysia, Korea, USA and Italy, respectively. Some Australian reports documented the syndrome predominantly in the Caucasian population, indicating an epidemiologic correlation to local virus circulation instead of genetic association.[16,19] Clinical surveillance in Europe demonstrated variable non-polio infection distribution across the years. An increased occurrence rate of 60% related to Echovirus 6 infection with neurological symptoms in patients younger than 7 years was documented in Netherlands from January until August 2016.[49]

Consciousness disturbance (CD; GCS<13) was the most common (93/165, 56.3%) neurological symptom in MERS patients, followed by seizures (77/165, 46.6%) and delirious behavior (DB) (55/165, 33.3%). As described by Kashiwagi et al.[5], DB symptoms are divided as follows: visual hallucination, nonvisual sensory misperceptions, emotional changes (such as laughter and fear), incoherent speech, purposeless movements, and impulsive behavior. Among the 55 cases with DB, clear delirium occurred in 13/55 (23.6%), irritability in 13/55 (23.6%), hallucinations in 5/55 (9.1%), purposeless movements in 4/55 (7.3%) and abnormal behavior in 3/55 (5.4%). Movement disorders were described in 16/165 patients (9.7%), mainly ataxia in 12/16 (75.0%), tremor in 3/16 (18.7%) and gait disturbance in 1/16 (6.2%). Speech impairment was reported in 16/165 patients (9.7%), dysarthria in 5/16 (31.2%), slurred speech in 5/16 (31.2%), abnormal speech in 5/16 (31.2%), and mutism in 2/16 (12.5%). Motor deficits were described in 11/165 (6.6%) patients, 5/11 (45.4%) showed signs of motor deterioration, 2/11 (18.2%) muscle weakness, 1/11 (9.1%) upper arm paresis, 1/11 (9.1%) lower arm sensorimotor polyneuropathy, 1/11 (9.1%) dominant hemiplegia and 1/11 (9.1%) akinetic mutism. Cranial nerve deficits such as eye movement disorders, ophthalmoplegia and strabismus were reported in 4/165 patients (2.4%), blindness in 3/165 (1.8%), dizziness in 2/165 (1.2%), facial palsy in 1/165 (0.6%) and pseudobulbar palsy in 1/165 (0.6%).

Fever (117/165, 70.9%) was the most common non-neurological prodromal symptom, followed by gastrointestinal symptoms such as abdominal pain, vomiting and diarrhea (77/165, 46.6%), cough (29/165, 17.6%) and headache (21/165, 12.7%). Only one patient had clinical signs of sepsis.[50]

MERS-associated infectious agents were identified in 106/165 patients (64.2%): RV in 26/165 (15.7%), *Mycoplasma pneumoniae* in 19/165 (11.5%), influenza A in 14/165 (8.5%), mumps virus in 8/165 (4.8%), adenovirus in 6/165 (3.6%), influenza B in 6/165 (3.6%), CMV in 3/165 (1.8%), *Enterococcus faecalis* in 3/165 (1.8%), EBV in 3/165 (1.8%) - one had also an EBV-related hemophagocytic lymphohistiocytosis - herpesvirus in 2/165 (1.2%), coxsackie virus in 2/165 (1.2%), Echovirus in 2/165 (1.2%), *Escherichia coli* in 2/165 (1.2%), parainfluenza virus, *Salmonella* gastroenteritis, HHV-6 infection, *Campylobacter jejuni*, *Klebsiella pneumoniae*, parvovirus B19, respiratory syncytial virus, dengue virus, *Streptococcus pneumoniae* and group B *Streptococcus* in only 1 patient (0.6%), respectively. MERS was

Table I. Pediatric Cases of Mild encephalopathy with reversible splenial lesion.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
Kobata R. et al. 2002	1	2	F	Consciousness disturbance	Fever, diarrhoea, vomiting	Rotavirus	NE	NE	Type I	DZP	CR
Takanashi J. 2004	2	7	F	Drowsiness, hallucination	Fever, cough, rinorrhea	Influenza A (H3)	N	N	Type I	Acetaminophen	CR
	3	11	M	Right sided dominant paralysis	Fever, cough, rhinorrhea	Influenza B	N	N	Type II	Acetaminophen, Amanthadin	CR
	4	3	F	Seizure, motor deterioration	Diarrhoea, vomiting	UK	Pleocytosis	SBA	Type I	Dex, PB	CR
	5	2	M	Seizure, drowsiness	Fever	UK	N	SBA	Type I	Diazepam	CR
	6	4	F	Seizure, blindness	Fever, diarrhoea	UK	NE	SBA	Type I	Diazepam	CR
	7	5	M	Seizure, delirium	Fever	Influenza A	N	SBA	Type I	-	CR
	8	5	M	Seizure, delirium	Fever	Adenovirus	N	SBA	Type I	IVIG	CR
Tada H. et al. 2004	9	7	M	Delirium	Fever, parotitis	Mumps	Pleocytosis	SBA	Type I	IVIG	CR
	10	8	M	Delirium, seizure	Headache, fever, vomiting	Mumps	Pleocytosis	N	Type I	-	CR
	11	4	F	Seizure, delirium	Fever	UK	N	NE	Type I	Antibiotic, Diazepam	CR
	12	9	F	Neck stiffness, rigor, tremor	Fever	UK	Pleocytosis	SBA	Type I	Acyclovir, Antibiotic, Dex	CR
	13	10	M	Drowsiness	Fever	UK	N	SBA	Type I	Antibiotic, IVIG	CR
Natsume et al. 2006	14	2	F	Seizure	Diarrhoea, vomiting	Rotavirus	ND	N	Type I	DZP,PB	CR
	15	6	M	Headache, delirious behavior	Fever, vomiting	UK	N	N	Type II	-	CR
	16	8	M	Drowsiness	Fever	UK	Pleocytosis	RD	Type II	Acyclovir	CR
Takanashi J. et al. 2006	17	4	F	Drowsiness, seizure	Fever	EBV	N	DSW	Type II	Acyclovir	CR
	18	5	F	Drowsiness, seizure	Fever	UK	N	N	Type II	PSL	Mental delay (Frontal Atrophy)
Matsubara K. et al. 2007	19	12	F	Headache, consciousness disturbance, muscle weakness	Fever	Influenza B	N	FSW	Type I	PSL	CR
Ganapath-y S. et al. 2008	20	12	M	Drowsiness, delirious behavior	Fever, headache	Influenza B	N	SBA	Type I	-	CR
Tokunaga Y. et al. 2008	21	8	F	Ataxia, muscle weakness, tremor	Fever, cough	M. Pneumoniae	NE	NA	Type I	-	CR
Hashimoto Y. et al. 2009	22	3	M	Drowsiness, up-deviation eight, hypotonia	Fever, vomiting, diarrhoea	UK	Pleocytosis, ▲P	DSW	Type I	Acyclovir	CR (SCC lesion until 154 d-Gliosis)
Ohgoshi Y. et al. 2009	23	10	F	Drowsiness	Cough	M. Pneumoniae	NE	NA	Type I	NA	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
Fukuda et al. 2009	24	2	M	Consciousness disturbance	Fever, vomiting, diarrhoea	Rotavirus	NA	DSW	Type I	PSL	CR
Kato et al. 2009	25	1	F	Seizure	Fever, vomiting, diarrhoea	Rotavirus	NA	IS	Type I	DZP	CR
Fluss J. 2009	26	2,5	F	Hipotonia, refusal of walking, irritability, dysartria consciousness disturbance, mutism, ataxia.	Fever, cough	Influenza A	Pleocytosis	SBA	Type I	Acyclovir	CR
Imamura T. et al. 2010	27	6	F	Seizure, consciousness disturbance	Fever, sore throat	Adenovirus	N	N	Type II	MDZ, PSL, Antibiotic,	CR
	28	2	M	Seizure, consciousness disturbance	Fever	UK	N	NA	Type II	Antibiotic, Dex	CR
Jang Y.Y. et al. 2010	29	2,5	F	Seizure	Vomiting, diarrhoea	Rotavirus	NE	N	Type I	Acyclovir	CR
Iwata A. et al. 2010	30	14	M	Dysarthria, dysphagia, mild ptosis (Pseudobulbar Palsy)	Fever, cough, headache, fatique	Influenza A (H1N1)	N	NA	Type II	Zanamivir	CR
Kubo K. et al. 2010	31	12	F	Abnormal behavior, drowsiness, seizure	Fever	M. Pneumoniae	NA	NA	Type I	Steroid	CR
Takanashi J. et al. 2010	32	10	M	Seizure, drowsiness	Fever	UK	N	FSW	Type II	Steroid, Acyclovir	CR
	33	6	M	Delirious behavior, drowsiness, consciousness disturbance	Fever, cough, rhinorrhea	UK	N	FSW	Type II	Zanamivir	CR
Arawaka et al. 2010	34	4	F	Consciousness disturbance	Diarrhoea, vomiting	Rotavirus	NA	NE	Type I	Supportive	CR
	35	3	M	Consciousness disturbance	Fever, vomiting	Rotavirus	NA	NE	Type I	Supportive	CR
Osuka S. et al. 2010	36	3	F	Drowsiness, seizure	Fever, vomiting, diarrhoea	M. Pneumoniae	N	NA	Type I	Antibiotic	CR
	37	8	M	Ataxia, mental confusion, drowsiness, lethargy	Fever	M. Pneumoniae	N	NA	Type I	Antibiotic, Steroid	CR
Hara M. et al. 2011	38	8	M	Delirious behavior	Fever, vomiting	Mumps vaccination	Pleocytosis	NA	Type II	mPSL	CR
Itamura S. et al. 2011	39	14	F	Delirious behavior	Fever, headache, chest pain	Kawasaki D.	N	N	Type I	IVIG	CR
Nakamoto T. et al. 2012	40	6	F	Delirium	Cough, fever	M. Pneumoniae	NE	NA	Type I	Antibiotic	CR
Morichi S. et al. 2012	41	9	M	Seizure, delirium	Fever, coughing, nasal discharge	Influenza A	N	DSW	Type II	Oseltamivir. mPSL	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
	42	8	M	Delirious behavior, drowsiness	Fever	Kawasaki D.	N	FSW	Type I	IVIG, CY, IFX	CR
	43	7	F	Delirious behavior, drowsiness	Fever	Kawasaki D.	N	N	Type I	IVIG	CR
Takanashi J. et al. 2012	44	10	F	Delirious behavior, drowsiness	Fever	Kawasaki D.	N	N	Type II	IVIG	CR
	45	2	F	Delirious behavior, drowsiness	Fever	Kawasaki D.	N	DSW	Type I	IVIG, mPSL	CR
	46	14	F	Delirious behavior, drowsiness	Fever	Kawasaki D.	Pleocytosis	DSW	Type I	IVIG	CR
	47	7	F	Delirious behavior, drowsiness	Fever	Kawasaki D.	N	DSW	Type I	IVIG	CR
Sato T. et al. 2012	48	7	F	Consciousness disturbance, delirious behavior	Right neck pain, fever, vomiting, diarrhoea	Kawasaki D.	N	DSW	Type I	Antibiotic, IVIG	CR
	49	1	F	Seizure	NA	UK	N	NA	Type I	Antiepilept	NA
	50	2	F	Seizure	NA	UK	N	NA	Type II	Antiepilept	NA
Miyata R.	51	2	M	Seizure	NA	Influenza A	N	NA	Type I	Antiepilept	NA
et al. 2012	52	3	F	Seizure	NA	UK	N	NA	Type II	Antiepilept	NA
	53	6	M	Seizure, delirious behavior	NA	RS Virus	N	NA	Type I	Antiepilept	NA
	54	13	F	Seizure	NA	Influenza A	N	NA	Type I	Antiepilept	NA
Uchida Y. et al. 2013	55	7	M	Abnormal speech, drowsiness	Cough, fever	M. Pneumoniae	Pleocytosis	N	Type II	Antibiot, Steroid	CR
Kometani H. et al. 2013	56	6	M	Consciousness disturbance, delirious behavior	Fever, headache	E. Faecalis Pyelonephritis	N	DSW	Type II	Antibiotic	CR
	57	9	M	Seizure, Consciousness disturbance, Delirious behavior	Fever, vomiting	E. Faecalis Pyelonephritis	Pleocytosis	NA	Type I	Antibiotic	CR
Matsuoka T. et al. 2013	58	4	M	Seizure, delirious behavior	Vomiting, diarrhoea,	Rotavirus	N	N	Type I	Antiepilept	CR
Okamoto T. et al. 2014	59	16	F	Delirium, consciousness disturbance	Fever, headache, back pain	K. Pneumoniae Pyelonephritis	N	NE	Type I	Antibiotic	CR
Haplern L.A. et al. 2013	60	5	M	Consciousness disturbance, seizure	Fever, cough	Parainfluenzae virus	Pleocytosis	SBA	Type II	Antibiotic	CR
Fuchigami T.et al. 2013	61	4	F	Consciousness disturbance, seizure	Vomiting, diarrhoea	Rotavirus	N	DSW	Type I	mPSL Diuretic	CR
Yokoyama et al. 2013	62	2	M	Seizure	Fever, vomiting, diarrhoea	Rotavirus	NA	N	Type I	PB	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
Notebaert A.et al. 2013	63	13	M	Abnormal speech, ataxia, confusion, drowsiness, lethargy	Abdominal pain, fever	M. Pneumoniae	Pleocytosis	DSW	Type II	NA	CR
Kashiwagi M. et al. 2014	64	2,75	M	Seizure, dysarthria, delirious behavior, consciousness disturbance	Fever	Influenza A	N	DSW	Type II	mPSL, MDZ, Mannitol, DZP, Oseltamivir	CR
	65	3,25	F	Seizure, dysarthria, delirious behavior, consciousness disturbance	UK	Influenza A	N	DSW	Type I	mPSL, Mannitol	CR
	66	7,75	F	Consciousness disturbance	UK	Influenza A	ND	DSW	Type I	mPSL, Mannitol	CR
	67	10,7	F	Delirious behavior, consciousness disturbance	UK	Kawasaki D.	N	DSW	Type II	PB, mPSL	CR
	68	6,25	M	Delirious behavior, consciousness disturbance	UK	Kawasaki D.	ND	N	Type I	mPSL	CR
	69	5	M	Delirious behavior, seizure, Consciousness disturbance	Enterocolitis, diarrhoea	Rotavirus	N	DSW	Type II	mPSL	CR
Suzuki H. et al. 2014	70	11	M	Abnormal behavior	Fever, (HLH)	Parvovirus B19	N	DSW	Type I	IVIG	CR
Hatanaka M.et al. 2014	71	17m	F	Seizure, consciousness disturbance	Fever, AESD	HHV-6	N	N	Type I	mPSL,MDZ, DZP,IVIG	CR
Shah S. et al. 2014	72	2	M	Seizure	Fever, cough	Influenza A	N	N	Type I	Oseltamivir. Clobazam	CR
Watanabe T.et al 2014	73	6m	M	Consciousness disturbance	Fever, renal dysfunct. (Fanconi s.)	UK	N	N	Type I	Supportive	CR
Mazur-Meleska K. et al. 2015	74	6	F	Seizure	Fever, diarrhoea	Rotavirus	ND	FSW	Type I	Dex	CR
Karampatsas K..et al. 2015	75	4	M	Consciousness disturbance	Vomiting, diarrhoea, fever	Rotavirus	N	DSW	Type I	Antibiotic	CR
Pan J.J. et al. 2015	76	18	F	Headache	Fever	UK	Pleocytosis	NA	Type I	mPSL+Dex, IVIG	CR
	77	2	F	Seizure	Fever	Rotavirus	NA	NA	Type I	mPSL+Dex, IVIG	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
	78	3	M	Irritability, lethargy, ataxia	Fever, cough	UK	NA	NA	Type II	Antibiotic, Acyclovir	CR
	79	6	F	Irritability, lethargy	Fever, coryza, headache, vomiting, abdominal pain	Kawasaki D.	NA	NA	Type I	IVIG, Aspirin, Antibiotic	CR
	80	5	F	Drowsiness, confusion, slurred speech, seizure, ataxia	Fever,vomiting	UK	NA	NA	Type I	mPSL, MDZ	CR
Ka A. et al. 2015	81	7	F	Drowsiness, confusion, visual hallucinations	Fever, headache, abdominal pain, vomiting, bloody diarrhoea	Salmonella	NA	NA	Type I	Antibiotic, Acyclovir	CR
	82	9	M	Irritability, slurred speech, confusion, ataxia	Fever, vomiting	CMV	NA	NA	Type II	mPSL, Antibiotic	CR
	83	5	F	Lethargy, ataxia	Fever, vomiting, cough	Influenza B	NA	NA	Type II	None	CR
	84	4	M	Confusion, slurred speech, hallucinations, ataxia	Fever, abdominal pain,cough, coryza, conjunctiv.	Adenovirus	NA	NA	Type I	Antibiotic, Acyclovir	CR
	85	9	M	Consciousness disturbance	Fever, vomiting	Mumps vaccination	Pleocytosis	FSW	Type II	NA	CR
	86	5	M	Delirium, seizure	Fever, vomiting, headache	Mumps vaccination	Pleocytosis	FSW	Type II	NA	CR
Takanashi J. et al.2015	87	2	M	Consciousness disturbance, dysarthria	Fever	Mumps vaccination	Pleocytosis	N	Type I	NA	CR
	88	8	M	Delirium	Fever, vomiting, headache	Mumps vaccination	Pleocytosis	N	Type II	NA	CR
	89	1	M	Consciousness disturbance, seizure	Fever, vomiting	Mumps vaccination	Pleocytosis	DSW	Type I	NA	CR
Kawagoshi R. et al. 2015	90	6	M	Drowsiness, irritability	Fever, cough, headache	M. Pneumoniae	Pleocytosis	DSW	Type I	Antibiotic	CR
	91	8	M	Drowsiness, consciousness disturbance	Fever	Influenza A	NA	DSW	Type I	IVIG, mPSL	CR
Azuma J. et al. 2016	92	3	F	Drowsiness, consciousness disturbance, seizure	Fever	E. faecalis	NA	DSW	Type I	Antibiotic	CR
	93	2	F	Consciousness disturbance, seizure	Fever, vomiting	Rotavirus	NA	FSW	Type I	mPSL	CR
Fong C.Y.et al. 2016	94	14	F	Delirium, ophtalmoplegia, consciousness disturbance	Fever	Dengue v. type II	UK	NA	Type I	Supportive	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
Fang Q.et al. 2016	95/123	4±3,6	M/F 17/12	Consciousness disturbance (18 pts), Seizure (18 pts)	Fever	Rotavirus 5 pts, M. Pneumoniae 4 pts, HSV 2 pts, Coxsackie 2 pts, Adenovirus 2 pts, Echovirus 2 pts, Influenza A 1 pt, CMV 1 pt, EBV 1 pt, UK 9 pts	Pleocytosis and ▲P in 3 pts	NA	Type I 24 pts; Type II 5 pts	Antiviral 3 pts, Steroid 7 pts, IVIG 2 pts, Antiepileptic 1 pt	CR
Hirayama Y.et al. 2016	124/126	4,2	M/F 2/1	NA	NA	Influenza 1 pt, UK 2 pts	NA	NA	NA	NA	CR
Hosoda A. et al.2016	127	3	F	Seizure	Clinical signs of sepsis	GBS	N	DSW	Type I	Antibiotic, Diazepam	Brain Atrophy, Temporal regression of motor function
Ikeno M. et al. 2016	128	14	M	Consciousness disturbance, CIP	Headache, gastric perforation,	UK	Pleocytosis, ▲P	DSW	Type I	mPSL	CR
Ueda N. et al. 2016	129	14	M	Abnormal speech, hallucinations, delirious behavior, drowsiness	Fever, cough	M. Pneumoniae	ND	NE	Type I	mPSL, Acyclovir	CR
	130	8	F	Drowsiness, lethargy, ataxia, tremors	Cough, headache, vomiting, diarrhoea	M. Pneumoniae	ND	N	Type II	Antibiotic	CR
Avcu G. et al. 2016	131	10	M	Consciousness disturbance, motor automatism	Fever, vomiting, lethargia	S. Pneumoniae	Pleocytosis, ▲P	N	Type I	Antibiotic, Acyclovir	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
	132	2,9	M	Seizure, irritability, motor deterioration, slurred speech	Fever, vomiting, abdominal pain	M. Pneumoniae	N	N	Type I	None	CR
	133	6,6	M	Headache, delirium, stupor, slurred speech, neck stiffness, drowsiness	Fever, vomiting, abdominal pain	M. Pneumoniae	N	SBA	Type I	mPSL, IVIG	CR
	134	3	F	Seizure, irritability, motor deterioration	Fever, vomiting, diarrhoea, cough	Rotavirus	N	SBA	Type I	Dex,PB, IVIG	CR
	135	2,3	F	Ataxia	Fever, vomiting, MLNE, diarrhoea, lip and knee-joints effusion	Rotavirus	N	N	Type I	Dex, IVIG	CR
	136	3,7	F	Seizure, hallucination	Cough, diarrhoea, vomiting, abdominal pain, MLNE	Rotavirus	N	SBA	Type I	-	CR
Chen W.X. et al. 2016	137	7	M	Drowsiness	Fever, vomiting, headache	Adenovirus	N	N	Type I	-	CR
	138	2,4	F	Seizure	Vomiting, diarrhoea, cough	BJ Campylobacter	N	N	Type I	DZP, PB	CR
	139a	10m	M	Seizure, irritability	Fever, cough, vomiting	UK	N	N	Type I	Dex, IVIG	CR
	139b	1	M	Seizure, irritability, stupor, drowsiness, motor deterioration	Diarrhea, fever, vomiting	UK	N	IS	Type II	LEV, PB	ID
	140	2,4	F	Seizure, irritability	Diarrhoea, vomiting	Rotavirus	N	SBA	Type I	mPSL	CR
	141	1,4	F	Seizure, irritability	Diarrhoea, cough, vomiting	Rotavirus	N	N	Type I	DZP	CR
	142	2	M	Seizure, irritability, motor deterioration	Fever, vomiting	UK	N	SBA	Type I	MDZ	CR
	143	10,5	M	Dizziness	Cough, fever	Influenza A	ND	NE	Type I	None	CR
	144	5	F	Seizure, abnormal behavior, consciousness disturbance	Fever, vomiting, abdominal pain, afbn	E. Coli	N	DSW	Type I	Antibiotic,Dex,	CR
Dong K. et al. 2016	145	14	F	Signs suggestive of transient ischemic attack (tia)	Flu-like symptoms	UK	N	DSW	Type II	-	CR
Yuan ZF et al. 2016	146	9	M	Drowsiness, left peripheral facial nerve paralysis, lethargy	Fever, headache, vomiting, macupapular rash	M. Pneumoniae	N	DSW	Type I	Dex,Antibiotic, Mannitol	CR
	147	12	M	Drowsiness, lethargy, dizziness	Cough, headache, vomiting	M. Pneumoniae	N	DSW	Type I	Dex, Antibiotic, Mannitol	CR

Table I. Continue.

Authors and year	n	Age (yrs)	Sex	Neurological symptoms	Prodromal symptoms	Etiology	CSF	EEG	MRI	Treatment	Prognosis
Kurokawa Y. et al. 2017	148	2	F	Seizure, consciousness disturbance	Fever	Kawasaki D.	NA	DSW	Type I	IVIG, mPSL, IFX	CR
Britton P. N. et al. 2017	149	5	F	Lethargy, unsteady gait	Fever, vomiting	Influenza B	ND	NE	Type I	-	CR
Sun D. et al. 2017	150	2d	M	Poor reactivity, tic of limbs	Decreased reactivity	UK	N	N	Type II	Antibiotic	CR
	151	3d	M	Gaze palsy and shaking of limbs	Decreased reactivity	UK	N	NA	Type II	Antibiotic,PB	CR
	152	12d	M	Limb hyperspasmia	-	UK	N	IS	Type II	Antibiotic, PB	CR
	153	3d	M	Seizure	-	UK	N	N	Type I	Antibiotic	CR
	154	1d	M	Groaning and irritability	-	UK	N	N	Type II	Antibiotic	CR
Yagamuci H. et al.2017	155	3	F	Gait disturbance, delirium, consciousness disturbance, irritability	Fever, abdominal pain	EBV-HLH	N	NA	Type II	HLH -2004 Regimen	CR
Feraco P.et al.2017	156	22m	M	Febril seizures, afebril seizures, drowsiness	Fever	CMV	N	DSW	Type I	Levetiracetam, Ganciclovir	CR
Vanderscheren G.et al 2018	157	16	M	Lethargy, akinetic mutism	Fever, cough	Influenza B	N	SBA	Type II	-	CR
Yildiz A.E.et al 2018	158/165	5,9	M/F 5/3	Seizure(4), Delirious Behavior (1), Drowsiness(1), Ataxia(1),Transient blindness(2),Abnormal speech(2), Headache(1)	Nausea and vomiting (6), Diarrhea(6), Fever(3)	Rotavirus 1 pt, E.Coli 1pt	N 6pts; NA in 2 pts	DSW in 1 pt	Type I 7 pts; Type II 1 pt	Ceftriaxone, Acyclovir 2 pt (for 2 days)	CR
Our case		4,9	F	Gait disturbance, lethargy, dysarthria, consciousness disturbance, strabismus, gaze paresis, muscle weakness	Fever, diarrhoea	ECHO-Virus 6	Pleocytosis, ▲P	SW	Type I	Antibiotic, Acyclovir Methilpred, Prednisolon	CR

A: abnormal, AESD: mild form of acute encephalopathy with biphasic seizures and late reduced diffusion, AFBN: acute focal bacterial nephritis, Antiepileptic: antiepileptic drugs, BA: background activity, CIP: critical illness polyneuropathy, CR: clinical recovery, CY: cyclosporine, d: days, Dex: Dexamethasone, DSW: diffuse slow wave, DZP: diazepam, FSW: focal slow wave, HLH: Hemophagocytic lymphohistiocytosis, ID: intellectual disability, IFX: infliximab, IVIG: intravenous immunoglobulin, IS: intermittent spikes, m: months, MDZ: midazolam, MNLE: mesenteric linphonode enlargement, mPSL: methylprednisolone, NA: not available, NE: not examined, N: normal, ND: not done, ▲P: high CSF proteins, PB: phenobarbital, PSL: prednisolone, pts: patients, RD: rolandic discharge, RS virus: Respiratory Syncytial virus, SBA: slow background activity, SCC: Splenium of the corpus callosum, UK: unknown.

associated with Kawasaki disease in 12/165 (7.3%) patients. Microbiologic and serologic examinations were negative in 59/165 (35.7%) patients, and no infectious pathogens were identified in these cases.

We analyzed the association between etiological agents and symptoms. CD symptoms 93/165 (56.4%) were most frequently related to *Mycoplasma pneumoniae* in 12/93 (12.9%) patients, RV in 8/93 (8.6%) and influenza virus in 6/93 (6.4%). About patients developing seizures (77/165, 46.7%), RV infection was identified in 14/77 (18.2%) and influenza in 6/77 (7.8%). Considering cases with DB symptoms (55/165, 33.3%) the most frequent etiological agents were influenza A virus in 7/55 patients (12.7%), RV in 6/55 (10.9%) *Mycoplasma pneumoniae* in 6/55 (10.9%) and mumps virus in 5/55 (9.0%). In 10/55 of patients with DB (18.2%) Kawasaki disease was confirmed. Movement disorders described in 16/165 cases (9.7%) occurred most frequently in patients with *Mycoplasma pneumoniae* infections (4/16, 25.0%), and all these cases had ataxia. Out of 16/165 cases characterized by speech impairment (9.7%), the most frequent pathogens identified were *Mycoplasma pneumoniae* in 5/16 (31.2%), influenza A virus in 4/16 (25.0%), influenza B in 1/16 (6.2%), CMV in 1/16 (6.2%), adenovirus in 1/16 (6.2%), and mumps virus in 1/16 (6.2%). In 4/5 cases (80.0%) with dysarthria an association with influenza A virus was demonstrated. Mutism was reported in 2 patients with influenza virus (A in 1 case and B in the other one).

Lumbar puncture was performed in 135/165 (81.8%) patients, and CSF pleocytosis (>10 WBCs/μl) was diagnosed in 24/165 (14.5%) patients, 7/24 (29.2%) showed increased protein levels. 17/24 (70.8%) CSF pleocytosis patients were described as MERS type I and 7/24 (29.2%) patients as type II. No correlation between pleocytosis and worse outcome could be observed. CSF pleocytosis patietns had the following infections: mumps virus in 8/24 (33.3%), *Mycoplasma pneumoniae* in 3/24 (12.5%), *Enterococcus faecalis* in 1/24 (4.2%), *Streptococcus pneumoniae* in 1/24 (4.2%) and human parainfluenza virus type 3 in 1/24 (4.2%). In 2 patients, persistent pleocytosis were described for a period of more than 5 months.[51-52] Identification of the infectious agent by RT-PCR on CSF specimens was performed in only 6 patients with mumps-related MERS,[31-32] while in other patients diagnosis was achieved with a blood serological test or RT-PCR with throat swab. CSF glucose was normal in all cases.

Considering EEG, in 60/165 patients (36.4%) EEG findings were abnormal: focal slow waves were described in 8/60 (13.3%) (occipital waves in 5, parieto-occipital, temporo-occipital and frontal waves in 1, respectively); EEG revealed diffuse slow waves in 31/60 (51.7%) (authors described high voltage slow wave in 7 cases), slow background activity in 17/60 (28.3%), intermittent spikes in 3/60 (5.0%), and rolandic discharge in 1/60 (1.7%). Analyzing the association between EEG results and etiological agents, influenza virus (both A and B) was observed in 8/60 (13.3%), RV in 7/60 (11.7%), mumps virus in 4/60 (6.7%), adenovirus, EBV, CMV, *Escherichia coli* and *Enterococcus faecalis* in 1/60 (1.7%), respectively. Analyzing the association between EEG results and clinical syndrome diagnosis of Kawasaki disease was found in 6/60 patients (10.0%) with EEG abnormalities. Between patients with abnormal EEG findings, 38/60 (63.3%) had CD symptoms, 26/60 (43.3%) seizures and 19/60 (31.7%) DB. In all patients, follow-up EEG was normal, as also in our case. Clinical follow-up in these 60 patients revealed a good prognosis, except for one MERS type II case reported by Chen et al.[28], who developed intellectual disability.

Considering neuroimaging, 121/165 (73.3%) were diagnosed as MERS type I. Diagnosis of MERS type II was reported in 44/165 (26.7%) with hyperintensity lesions of CC in association with hyperintensity in the semioval center and parietal white matter bilaterally, or associated with diffuse hyperintensity of white matter (6 patients), or with hyperintensity in the center semiovale and periventricular symmetric hyperintense lesions (8 cases). In 3 (2.0%) cases, authors did not specify the extension

of hyperintensity lesions in the CC. Fluss et al.[21] described a MERS type II case with an additional restricted diffusion area of the right dentate nucleus suffering clinical mutism. In 2006, Takanashi et al.[3] reported a MERS type II with hyperintense asymmetric lesion in the gray matter of the prefrontal cortex with subsequent frontal atrophy and intellectual disability. Hyperintensity lesions in the SCC and in other brain areas on neuroimaging disappeared within 30 days in all cases, except in 1 patient with MERS type I, in whom the lesion could be still detected on brain MRI follow-up in T2-weighted imagines after 134 day. CSF analysis showed pleocytosis and increased proteins.[51]

Data about treatments revealed that 35/165 patients (21.2%) received antibiotic therapy after MERS onset, and 21/165 (12.7%) antiviral treatment. Intravenous immunoglobulin was administered to 23/165 (13.9%) patients, in 9 cases in association with corticosteroids. Eleven patients received, as steroid therapy, only Dexamethazone; 23 patients, methil-prednisolone (authors in 21 cases had specified a pulsed-dosed therapy; in 2 cases was prescribed also Dexamethazone) and 2 patients prednisolone. For 11 cases the corticosteroids treatment has not been specified. In 2 patients, infliximab was also administered (Table I).

The median recovery time was 13.3 days for MERS type I (though data about recovery time was only for 103/121 (85.1%) patients available) and 12.6 days for MERS type II (data about recovery time was for 34/44 (77.3%) patients available).

Regarding prognosis, all patients completely recovered within 30 days, except for 4 patients. A long- term follow-up showed intellectual disability in 2 MERS type II cases.[3,28] Notably, one of these patients had recurrent MERS episodes; the other patient showed brain lesions in regions usually not involved in MERS, as the prefrontal cortex and white matter. Another patient with MERS type I associated with recurrent *Streptococcus* group B sepsis had mild brain atrophy and motor function regression, which improved gradually in the long-term.[50] Notebaert et al.[44] described one *Mycoplasma pneumoniae*-related MERS type II case with residual ataxia and speech impairment, who fully recovered 4 months later. Fluss et al.[21] described one case of influenza A-related MERS with a cerebellar lesion (in the right dentate nucleus) on MRI, presenting with dysarthria and ataxia; in this patient clinical recovery was obtained 1 month later.

Our literature review revealed two cases in which MERS and other encephalopathies overlapped. One case described, additional to MERS, febrile infection-related epilepsy syndrome (FIRES), characterized by intractable seizures and the other case acute encephalopathy with biphasic seizures and reduced diffusion (AESD), characterized by recurrent complex partial seizures.[30,53]

The exact relationship between radiological evidence and clinical condition of MERS patients is still unclear. In a retrospective study, Tada et al.[2] excluded any correlation between neuro-radiological features of brain lesions and neurological symptoms. Ueda et al.[36] reported a longer clinical recovery time in MERS type II related to *Mycoplasma pneumoniae* infection than in type I, suggesting also a less benign course.

MERS pathogenesis is still unclear. Researchers hypnotized intramyelinic edema as a possible cause, which however cannot explain neonatal MERS occurrence considering the incomplete myelination in newborns.[1,22,29,54,55] Kawasaki disease, an acute febrile systemic vasculitis, has been described in association with MERS, demonstrating a possible correlation to immune system abnormalities triggering the pathogenesis.[53,56,57] Kometani et al.[58] reported a IL-6 elevation in the CSF of MERS patients associated with focal bacterial nephritis caused by *Enterococcus faecalis*. RT-PCR rarely detected infections in the CSF, suggesting an immune-mediated mechanism in MERS pathogenesis. In our review, direct causative agents in CSF were identified only in 6 patients.[31,32] Moreover, unknown genetic factors could

be likely involved, and indeed recurrent and familial cases of MERS are described in medical literature. Neuroradiological features in familiar forms are also characterized by a more extensive brain involvement then in sporadic MERS cases.[59,60]

Recently, MERS has been increasingly recognized in Caucasian children, although none of cases had a recognized Echovirus 6 infection, as our patient. Infections (viral in 58% of cases), but also systemic inflammatory diseases (as Kawasaki disease) can be associated with MERS. Neurological manifestations occur shortly after prodromal symptoms and neuroimaging consents to substantiate MERS diagnosis. A short follow-up is necessary to confirm the transient nature of splenial lesions. The therapeutic approach in MERS may vary on a case-by-case basis; it remains unclear if a specific therapy might change the clinical history of the disease. Data of our review demonstrate that MERS is a disease with an overall good prognosis, as almost all patients reported a complete recovery of neurological symptoms within 30 days irrespective of treatment. Considering the low number of MERS cases and different severity degrees, multicentre studies are needed to clearly elucidate its pathogenesis and define treatment guidelines.

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