Turkish Archives of Pediatrics

SCIENTIFIC LETTER
DOI: 10.5152/TurkArchPediatr.2021.21074

Mild Encephalitis/Encephalopathy With Reversible Splenial Lesion Due to *Enterococcus faecalis* in Children

Alberto Maria Cappellari[1], Laura Cozzi[2], Cristiano Gandini[3], Gaia Bruschi[2], Antonella Costa[4]

[1]Department of Neuroscience, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Lombardia, Italy
[2]UO Post-graduate School, Department of Pediatrics, University of Milan, Milan, Lombardia, Italy
[3]UO Department of Anesthesia and Intensive Care Woman-Child, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Lombardia, Italy
[4]UOC di Neuroradiologia, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Lombardia, Italy

Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is a clinico-radiologic disease included in the spectrum of reversible splenial lesion syndrome.[1,2] MERS is a transient encephalopathy associated with a reversible lesion of the splenium of corpus callosum (SCC) on magnetic resonance imaging (MRI) of the brain.[3,4] MERS is classified as type 1 when the involvement of SCC is isolated and type 2 when it occurs in association with extensive and/or entire callosal lesions.[1,3,5] MERS is caused by viral infections, including SARS COV-2 (severe acute respiratory syndrome coronavirus-2),[6] bacterial infections,[7,8] metabolic disorders,[3,5] electrolyte abnormalities,[7] and drugs.[1] Only 4 cases associated with Enterococcus infection have been reported.[3,7]

A 6-year-old African boy was hospitalized because of a prolonged seizure occurring with fever, followed by loss of consciousness, with normal age-appropriate blood pressure. His family history and past medical or neurological history were unremarkable. Neurological examination was consistent with acute confusional state, without nuchal rigidity or focal motor deficits.

Routine laboratory examination showed normal electrolytes, leucocyte count 13 760/mm^3 (normal: <10 000/mm^3), procalcitonin 100 ng/mL (normal values 0.2-0.6 ng/mL), and C-reactive protein 28.1 mg/dL (normal values 0-1 mg/dL). Cerebrospinal fluid (CSF) was normal, including cell count, glucose levels, and proteins. The initial treatment consisted of acyclovir and ceftriaxone, the first being stopped when CSF polymerase chain reaction by multiplex assay was negative for HSV-1.

Electroencephalography (EEG) recording began with the patient in the awake state and was characterized by a diffuse rhythm of 5 Hz that did not react to eye opening. The sleeping state was characterized by slow activity in the theta and delta range, without normal sleep patterns such as sleep spindles and K complexes. Brain MRI revealed a reversible splenial lesion associated with the characteristic "boomerang sign," which was evident in the SCC on fluid-attenuated inversion-recovery images (FLAIR), T2-weighted images (T2 WI), and diffusion-weighted images (DWI). No extra-callosal lesions or contrast enhancement were noted, consistent with MERS type 1 (Figure 1A-D). Spinal MRI was unremarkable, excluding other conditions that should be considered in the differential diagnosis of MERS, such as acute disseminate encephalomyelitis, multiple sclerosis, or neoplastic diseases. Autoimmune causes of encephalitis were excluded by extensive investigations on CSF and serum, including anti-GABA, anti-GAD, anti-VGKC, anti-AMPA, anti-NMDAR, anti-CASPR2, anti-LGI1, and anti-DPPX.

Urinary tract infection by *Enterococcus faecalis* was diagnosed (with colony count of 100 000 ufc/mL) and abdominal ultrasound revealed multiple renal abscesses (Figure 1H), in the absence of anatomic abnormality of the urinary system. Therefore, we decided to shift the therapy to ampicillin and amikacin, owing to high urinary concentrations generally achieved

Corresponding author: Alberto Maria Cappellari
✉albertocapp@yahoo.it
Received: March 28, 2021
Accepted: May 1, 2021

Cite this article as: Maria Cappellari A, Cozzi L, Gandini C, Bruschi G, Costa A. Mild encephalitis/encephalopathy with reversible splenial lesion due to enterococcus faecalis in children. *Turk Arch Pediatr.* 2021; 56(5): 527-529.

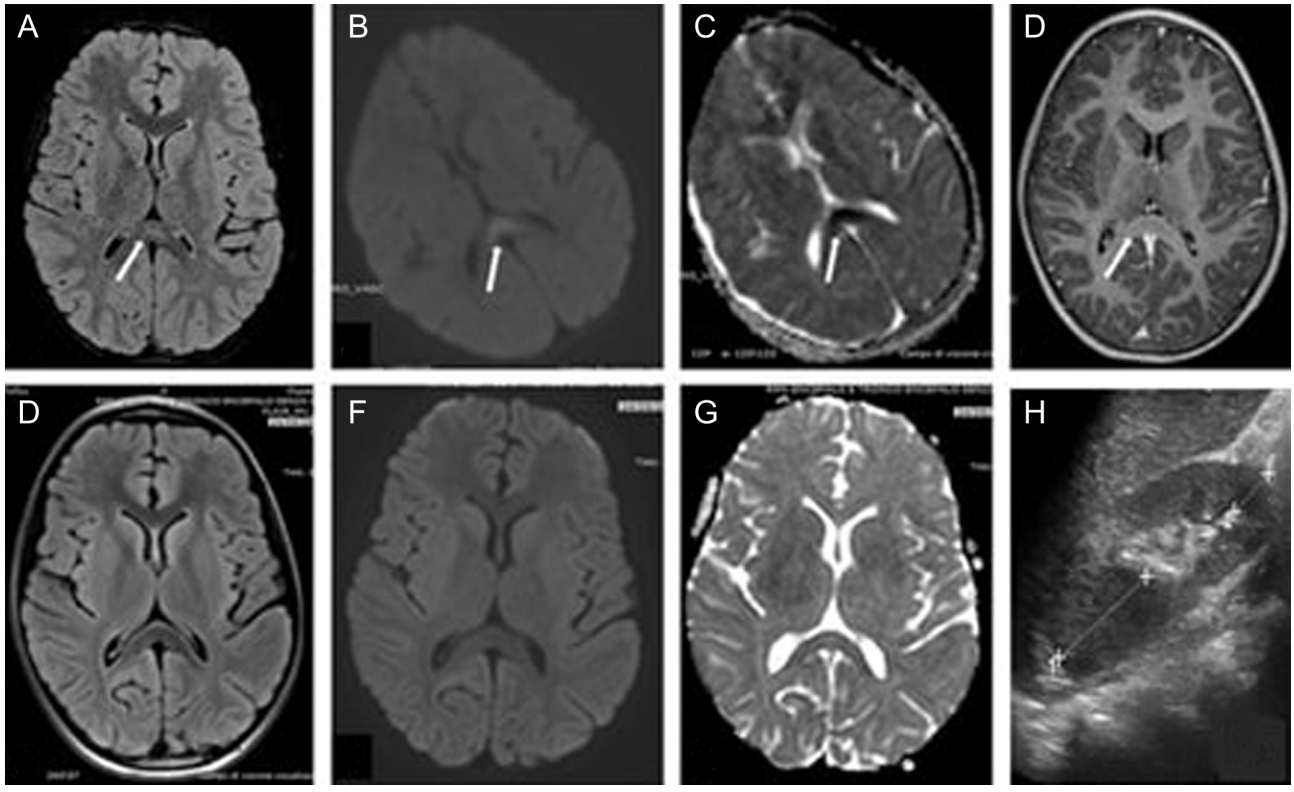

Figure 1. a-g. 3T initial MRI (A-D) of the patient revealed a lesion in the midline of splenium of corpus callosum with hyperintensity on FLAIR (A) and DWI (B), decreased apparent diffusion coefficient (ADC) values on ADC map (C) and isointensity without enhancement on conventional contrast-enhanced T1WI (D). Follow-up MRI (E-G) after 2 weeks showed resolution of the splenial lesion; no lesions were present on any sequence axial FLAIR image (E), DWI (F), ADC (G). Abdominal ultrasound revealed multiple renal abscesses (H). Ultrasonographic images of renal abscesses.

by aminopenicillins and possible usefulness of amikacin in the treatment of sepsis and meningitis, pending the results of blood and cerebrospinal fluid culture. After 1 week, considering the slow clinical improvement and decrease in the level of inflammatory markers, the infectious disease specialists suggested a treatment with meropenem. Neurological examination became normal after a few days, as well as EEG and brain MRI (Figure 1E-G). Antibiotic therapy was continued for 4 weeks. At the follow-up examination 1 year later, the child was in good health with a normal neurological examination.

The pathogenesis of MERS remains unclear.[1,3,8,9] Furthermore, the selective involvement of SCC is still to be explained. Inflammation of the corpus callosum or intramyelinic edema with separation of myelin layers were proposed to explain the pathogenesis of MERS. Serum and cerebrospinal interleukins (IL-10, 1L-6, interferon c) and urinary beta-2 microglobulin suggest an uncontrolled immune response.[10] Intramyelinic axonal edema has also been linked to water and electrolyte imbalance, mainly hyponatremia.[10] Hyponatremia (serum sodium level of less than 135 mmol/L) was reported by Takanashi et al. in MERS patients, and it was absent in the control groups.[10] Hypotonic hyponatremia causes an entry of water into the brain, resulting in cerebral edema. As the axons in the SCC are very tightly packed, it is possible that interstitial edema (water situated between the unmyelinated axons) could have reduced diffusion.[10] Molecular mimicry or antibodies induced by antigens with specific affinities for receptors in splenial axons or their myelin sheaths have been suggested to explain the isolated involvement of the splenium.[4] However, no clear data are available in current literature about which antigenic components of *Enterococcus faecalis* mimic SCC axons. Despite a number of hypotheses, further clinical, radiological, and genetic studies are necessary for a definite conclusion.[10]

The most common cause of reversible splenial lesion in childhood is infection-related MERS.[1,3] Various infectious agents, mostly viruses, are associated with MERS,[3] while bacterial infections have been reported in only about 3%[9] of patients. Among bacterial infections, *Mycoplasma pneumonia* is the most common agent related to MERS, while *Enterococcus faecalis* has been rarely reported. The literature data on *Enterococcus faecalis*-related MERS are summarized in Table 1.

The central nervous system can also be involved in urosepsis and septic shock. In fact, septic shock is often complicated by encephalopathy, cardiovascular autonomic failure, and neuroendocrine dysfunction. However, the pathogenetic mechanisms are different from those involved in MERS, including inappropriate immune–brain signaling, brain cell activation, deleterious production of nitric oxide, cell death, and dysfunction of intracellular metabolism.[11]

The most common neurological presentation of MERS is delirious behavior, followed by consciousness disturbance and new-onset seizures, all of which completely disappear in about a month.[1,3,5,8] MRI findings show transient splenial lesions with an abnormal signal on DWI-ADC (diffusion-weighted imaging

Table 1 . Summary of Literature Data on MERS Cases due to *Enterococcus faecalis* (Including the Case Described in the Present Article)

Author (Year)	Kometani (2014)[7]	Kometani (2014)[7]	Maruyama (2020)[3]	Maruyama (2020)[3]	Cappellari (Present Case)
Age (years)	6	8	8	11.5	6
Origin	Asian	Asian	Asian	Asian	African
Sex	M	M	M	M	M
Days of fever before MERS	<7	<7	2	5	2
Clinical presentation	i.s. ; i.	i.s. ; i.	i.s. ; i.	i.s. ; i. ; v.h.	l.o.c.
Seizure	Not present	g.t.c.	Not present	Not present	g.t.c.
MERS	Type 2	Type 1	Type 1	Type 1	Type 1
EEG	diffuse slow	alpha attenuation	diffuse slow	-	diffuse slow
Ureteral dilatation	Left	Right	-	-	Not present
Renal involvement	AFBN	AFBN	AFBN	AFBN	MRA
WBC (/μL)	27.800	20.100	13.800	11.500	13.760
CRP (mg/dL)	14.73	20.23	21.50	8.80	28.1
PCT (ng/mL)	-	-	-	-	100
Na (mEq/L)	129	134	137	134	140
CSF	Normal	Pleocytosis	Normal	Normal	Normal
Therapy	Antibiotic	Antibiotic	Antibiotic	Antibiotic	Antibiotic
Prognosis	CR	CR	CR	CR	CR
Recovery in days	-	-	4	3	5

M, male; i.s, incoherent speech; i, incontinence; v.h, visual hallucination ; l.o.c., loss of consciousness; g.t.c., generalized tonic–clonic seizure; AFBN, acute focal bacterial nephritis; MRA, multiple renal abscesses; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; CSF, cerebrospinal fluid; CR, complete recovery; - not determined.

and apparent diffusion coefficient),[4] FLAIR, and T2-WI[2]; the abnormalities typically do not show enhancement after contrast administration and resolve within 1-2 weeks.[1,3,4,5]

The prognosis of MERS is usually favorable,[1,4,8] and treatment is mainly related to the etiology.[8]

MERS should be considered in the differential diagnosis of children presenting with acute encephalopathy.[5] Clinicians should be aware of MERS since this is a treatable disorder.[3,7]

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – A.M.C., A.C.; Design -A.M.C., L.C.; Supervision - A.M.C., L.C., C.G.; Resource A.M.C., L.C.; Materials - A.M.C., L.C., A.C.; Data Collection and/or Processing - L.C., A.M.C., A.C.; Analysis and/or Interpretation - A.M.C., L.C.; Literature Search - A.M.C., L.C., G.B.; Writing - A.M.C., L.C., G.B., A.C.; Critical Reviews - A.M.C., L.C., C.G., A.C., G.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Chen WX, Liu HS, Yang SD, et al. Reversible splenial lesion syndrome in children: retrospective study and summary of case series. *Brain Dev*. 2016;38(10):915-927. [CrossRef]
2. Zhu Y, Zheng J, Zhang L, et al. Reversible splenial lesion syndrome associated with encephalitis/ encephalopathy presenting with great clinical heterogeneity. *BMC Neurol*. 2016;16:49. [CrossRef]
3. Maruyama Y, Sato M, Inaba Y, Fukuyama T. Comparison of mild encephalopathy with reversible splenial lesion with and without acute focal bacterial nephritis. *Brain Dev*. 2020;42(1):56-63. [CrossRef]
4. Zhang X, Chen N, Guo J, et al. Reversible splenial lesion syndrome in children: clinical analysis and summary of a case series. *J Int Med Res*. 2020;48(4):300060520914202. [CrossRef]
5. Ka A, Britton P, Troedson C, et al. Mild encephalopathy with reversible splenial lesion: an important differential of encephalitis. *Eur J Paediatr Neurol*. 2015;19(3):377-382. [CrossRef]
6. Bektaş G, Akçay N, Boydağ K, Şevketoğlu E. Reversible splenial lesion syndrome associated with SARS-CoV-2 infection in two children. *Brain Dev*. 2021;43(2):230-233. [CrossRef]
7. Kometani H, Kawatani M, Ohta G, et al. Marked elevation of interleukin-6 in mild encephalopathy with a reversible splenial lesion (MERS) associated with acute focal bacterial nephritis caused by Enterococcus faecalis. *Brain Dev*. 2014;36(6):551-553. [CrossRef]
8. Fang Q, Chen L, Chen Q, Lin Z, Yang F. Clinically mild encephalitis/ encephalopathy with a reversible splenial lesion of corpus callosum in chinese children. *Brain Dev*. 2017;39(4):321-326. [CrossRef]
9. Kasuga Y, Fuchigami T, Fukuda A, et al. Acute focal bacterial nephritis associated With central nervous system manifestations: a report of 2 cases and review of the literature. *Pediatr Emerg Care*. 2017;33(6):418-421. [CrossRef]
10. Takanashi JI, Imamura A, Hayakawa F, Terada H. Differences in the time course of splenial and white matter lesions in clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). *J Neurol Sci*. 2010;292(1-2):24-27. [CrossRef]
11. Sharshar T, Hopkinson NS, Orlikowski D, Annane D. Science review: the brain in sepsis–culprit and victim. *Crit Care*. 2005;9(1):37-44. [CrossRef]