Infant with Loeys-Dietz syndrome treated for febrile status epilepticus with COVID-19 infection: first reported case of febrile status epilepticus and focal seizures in a patient with Loeys-Dietz syndrome and review of literature

Asra Akbar, Sharjeel Ahmad, Sean Creeden, Huan Huynh

SUMMARY
Loeys-Dietz syndrome (LDS) is a rare, autosomal dominant multisystem disorder that is caused by mutations of transforming growth factor-β receptors. Mutations in SMAD3 and TGFB3 have been recently reported. LDS is characterised by the triad of arterial tortuosity, hypertelorism and a bifid uvula or cleft palate among other cardiovascular, craniofacial and orthopaedic manifestations. Patients with LDS show clinical and genetic variability and there is a significant risk of reduced life expectancy due to widespread arterial involvement, aortic root dilation, aneurysms and an aggressive vascular course. Thus early genetic testing is warranted if clinical signs and history are suggestive of this potentially catastrophic disorder. LDS predisposes patients to aortic aneurysms and early death due to vascular malformations, but neurological emergencies, such as seizures and febrile status epilepticus, have not been reported. Febrile status epilepticus is the most common neurological emergency in childhood. Neurological manifestations of COVID-19 in the paediatric population are not as well described in medical literature. To the best of our knowledge, this is the first reported case of febrile status epilepticus with COVID-19 infection in an infant with LDS. Our patient had focal epileptiform activity emanating over the left posterior hemisphere, which evolved into an electrographic seizure on video EEG. Such patients have a heightened risk of epilepsy in the future, and this occurrence is consistent with a diagnosis of focal epilepsy. Neurological complications such as epilepsy and status epilepticus in a patient with LDS have never been reported before. A brief review of literature is also given here.

BACKGROUND
Loeys-Dietz syndrome (LDS) is a rare connective tissue disorder that was first described by Loeys et al in 2005 in 16 people from 10 different families. The cause was attributed to heterozygous mutations in the genes encoding either type I or type II transforming growth factor-β, with resultant cardiac, vascular, craniofacial, skeletal and neurocognitive deficits. Phenotypical expression of LDS is present in patients who have mutations in the TGFB1, TGFB2, TGFB3 and SMAD3 genes. Genetic and clinical variability is found in the presentation of LDS.

Rapidly progressive aortic aneurysmal disease is frequently reported in LDS, specifically associated with transforming growth factor-β receptors (TGFBR) types I and II. LDS is also associated with skeletal fragility, osteoarthritis and low bone mass, eczema, asthma, allergies. LDS is associated with a higher prevalence of failure to thrive, constipation, eosinophilic gastrointestinal disease.

Vascular disease including tortuosity of arteries, aortic aneurysm and dissection is a life-threatening concern, and aneurysms and dissections in the carotid and verteobasilar systems require urgent treatment to prevent neurological complications such as strokes.

Cardiac manifestations, including congenital heart disease, bicuspid aortic valve, atrial septal defect, atrial fibrillation and mitral valve prolapse, have been reported.

Neurological problems, such as cognitive slowing and learning disability, are a rare manifestation in patients with LDS. Chiari malformation has been rarely reported in LDS and may exist with unrelated hydrocephalus. Dural ectasia is more frequently reported.

Headaches may be a feature of LDS, commonly found in 50% of cases, and it should be noted that vasoconstrictive medication is contraindicated given the tortuosity of arteries. Spinal deformity is a characteristic feature of LDS.

Febrile status epilepticus is the most common neurological emergency in childhood, which is frequently encountered in the critical care setting and can be refractory to treatment.

SARS-CoV-2 is the infectious agent responsible for COVID-19 and might have been the cause of febrile status epilepticus. A risk of cerebral stroke is heightened given the vascular malformation and arteries tortuosity; febrile seizures and/or epilepsy, however, have never been reported in patients with LDS.

CASE PRESENTATION
Our patient is an infant with a past medical history significant for biventricular hypertrophic cardiomyopathy, coarctation of the thoracic aorta and
innocuous infarction and endotracheal intubation in the neonatal intensive care unit. Family history was non-contributory.

At the age of 1 month, she was admitted owing to lethargy and poor oral intake and was diagnosed with left basal ganglia bleed. The presentation for status epilepticus was 2 months after the admission for the lethargy during which she was diagnosed with the basal ganglia bleed. There was a concern about possible non-accidental trauma, but investigations disclosed no information. There was no prior history of seizures, and a video EEG was read as normal. During that earlier admission at age of 1 month, the infant was found to have non- obstructive coarctation of the aorta and biventricular hypertrophic cardiomyopathy, bilateral internal carotid artery, eccentric mural thrombus of distal abdominal aorta, and uncontrolled hypertension. Once genetic testing had been completed and she was diagnosed with LDS, appropriate management was clear.

INVESTIGATIONS

At our facility a complete blood count showed an elevated platelet count of $739 \times 10^9/L$ (range $247 \times 10^9$–$580 \times 10^9$), and increased values of lactate acid $3.8 \text{ mmol/L}$ (range $0.90$–$1.80 \text{ mmol/L}$), D dimer $4.32 \mu \text{g/mL}$ (range $<0.50 \mu \text{g/mL}$), B-type natriuretic peptide $642 \text{ pg/mL}$ (range $<100 \text{ pg/mL}$), but not out of proportion to hypertrophy and dehydration. A complete metabolic panel showed low sodium of $134 \text{ mmol/L}$ (range $136$–$145 \text{ mmol/L}$); lactate dehydrogenase was $506 \text{ U/L}$ (range $125$–$220 \text{ U/L}$). Repeated D dimer and fibrinogen measurements were normal. Erythrocyte sedimentation rate, ferritin, protamine, international normalised ratio, triglycerides and C-reactive protein were normal, A respiratory FilmArray panel detected SARS-CoV-2. SARS-COV 2 nasopharyngeal PCR testing was positive. SARS-CoV-2 spike protein IgG was positive (2.16 S/C ratio; normal range $<1.45 \text{ S/C ratio}$).

Levels of copper, ceruloplasmin, renin, aldosterone, urine organic acids, serum amino acids, ammonia, carnitine and acylcarnitine were all normal. Cerebrospinal fluid analysis was non-revealing. Echo showed stable ventricular hypertrophy. Ultrasound of the renal artery did not show renal artery stenosis.

The skeletal survey at the earlier admission for lethargy and decreased oral intake did not show radiographic evidence of skeletal injury.

Video EEG at 72 hours during the admission for febrile status epilepticus and COVID-19 infection showed focal epileptiform activity over the left occipital, with maximal negativity at O1>P3>T5. The amplitude and frequency of the spikes increased and evolved to electrographic seizure on day 1 of the video EEG. The seizure lasted for about 2 min. No clinical signs were noted during this time (figure 1). No further seizures were reported for the next 2 days on video EEG. A MRI brain scan was obtained, which showed an interval increase in ventricular prominence and chronic haemorrhage breakdown products centred at the left lentiform nuclear region (figure 2). MR angiography showed significant tortuosity of the distal cervical segments of the internal carotid arteries bilaterally (figure 3). A MRI C spine scan showed abnormal signal of the cervical cord between the cervico-medullary junction and C7, consistent with cord oedema/injury (figure 4). CT angiography of the chest/abdomen and pelvis showed hypoplastic distal transverse arch of the thoracic aorta, hypoplastic distal abdominal aorta and mild non- obstructive coarctation of the thoracic aorta (figure 5). Genetic investigation revealed a heterozygous missense mutation in the TGFBR2 gene 3p24.1 c1715T>Cp.

Figure 1  Video EEG. Anteroposterior bipolar montage with 15s page showed repetitive left occipital epileptiform discharges (blue arrows), maximal negativity at O1>P3>T5. Amplitude and frequency are increased and evolved to electrographic seizure. The seizure lasted for about 2 min. No clinical signs were noted during this time.

Figure 2  (A) Axial non-contrast CT image of the head demonstrates a small round hyperdense haemorrhage within the left globus pallidus, with mild surrounding hypodense oedema. (B) Axial SWAN MR image of the brain confirms area of haemorrhage with prominent susceptibility artefact. (C) Axial T2-weighted MR image at the level of the centrum semiovale demonstrates diffuse abnormal white matter T2 hyperintensity. Brain MRI follow-up performed 2.5 weeks later, (D) Axial T2-weighted MR image at the level of the basal ganglia demonstrates increased size of the encephalomalacia/haemorrhage cavity and increased diffuse cerebral white matter volume loss with ventriculomegaly.
Leu572Pro (probably pathogenic) (Clinical Genome Centre, San Diego, California 92123, USA). The genetic report also showed variants of uncertain significance in the MYBPC3 gene (c.3103G>A p.A1a1035Thr) and in the Willebrand factor gene variant (c.7493c>Ap.AIa2498Asp).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis was broad given the patient’s presentation and multisystem involvement.

Menkes disease, which is a multisystem neurodegenerative and connective tissue disorder, was considered. Patients can present with tortuosity of bleed vessels and cerebral bleed as well as poor oral intake and hypotonia. In our patient given the tortuosity of the vascular artery and earlier clinical presentation, this disorder was thought to be possible. Other connective tissue disorders, such as Marfan syndrome, were considered in the differential diagnosis.

The possibility of non-accidental trauma was examined because of the cerebral bleed, but investigations showed no cause of non-accidental trauma and a skeletal survey was negative.

Meningitis was considered on the differential diagnosis, but the patient looked well and thus, febrile status epilepticus was thought to be in association with the COVID-19 infection.

Owing to dissection of the arteries and unknown causes of hypertension, other metabolic disorders were considered. The genetics service was consulted and a metabolic investigation was negative.

**TREATMENT**

The febrile status epilepticus resolved after the levetiracetam (Keppra) load and benzodiazepine was given. On arrival at this tertiary care centre, the Keppra dose was increased to 50 mg/kg/day divided twice daily and no further seizures were seen.

**OUTCOME AND FOLLOW-UP**

Our patient remained stable during the hospital course and no further seizures were reported. She was discharged home on levetiracetam. No further seizures have been reported since discharge. She has been diagnosed with motor delay and is receiving treatment for that. She has been eating and drinking well and is growing. Overall, according to the family, she is doing well.

**DISCUSSION**

Loeys-Dietz syndrome is an autosomal dominant connective tissue disorder that is clinically similar to, but more aggressive than, Marfan’s syndrome. It is caused by mutations of the

| Table 1 Types of Loeys-Dietz syndrome (LDS) and features | 1 2 14 26 27 |
|-----------------------------------------------|-------------------|
| Type  | Gene  | Common features                                      |
| LDS type 1 | TGFBR1 | Craniofacial features present                          |
| LDS type 2 | TGFBR2 | Minimal to absent craniofacial features and more cutaneous involvement |
| LDS type 3 | SMAD3 | Aneurysms-osteoarthritis syndrome                      |
| LDS type 4 | TGFBR | Aortic and cerebral aneurysms and skeletal manifestations |
| LDS type 5 | TGFBS | Low muscle mass, growth retardation                     |
| LDS type 6 | SMAD2 |                                                       |

Figure 3  (A) Non-contrast 3D time-of-flight MR angiography (MRA) 3D maximum intensity projection reformat shows tortuosity and mild narrowing of the proximal cervical internal carotid arteries, more prominent on the right with looping course (yellow arrows). (B) Follow-up MRA performed 2.5 weeks later demonstrates interval straightening and a more normal course of the cervical internal carotid arteries.

Figure 4  (A, B) Sagittal and axial T2-weighted MR images of the cervical spine demonstrate diffuse mildly expansile T2 hyperintense central spinal cord oedema and mild dural ectasia.

Figure 5  (A) 3D candy cane and (B) surface volume rendering maximum intensity projection reformats from the aortic root to the femoral arteries demonstrate mild hypoplasia and coarctation of the distal thoracic aortic arch, termination of the infrarenal abdominal aorta at the median sacral artery and hypoplasia/aplasia of the common iliac arteries, with collateral filling of the more distal major arteries of the lower extremities.
transforming growth factor-β (TGFβ) receptors. There is a genetic and clinical variability in the presentation of LDS. TGFβs are a group of multipotential cytokines that regulate cellular functions, including proliferation, migration and apoptosis.10

There are no specific diagnostic criteria for LDS and clinical diagnosis needs to be confirmed by a molecular genetic test.8 LDS was first reported as a mutation in the transforming growth factor-β receptor I (TGFBR1) and transforming growth factor-β receptor II (TGFBR2) genes.11 Subsequently, gene mutations in the mothers against decapentaplegic homolog 3 (SMAD3) gene and the transforming growth factor-β 2 ligand gene (TGFβ2) were identified and associated with LDS.12 13 (table 1)

LDS shows clinical and genetic variability associated with a significant reduction of life expectancy. The most common cause of death is rupture of aneurysms and arterial dissections.14 Neurological emergencies reported in association with SARS-CoV-2 infection and has a high rate of mortality (between 5% and 39%).15

Febrile status epilepticus is a neurological emergency and a risk factor for later development of epilepsy.9 Febrile status occurs in approximately 5% of febrile seizures and accounts for about 25% of all childhood cases of status epilepticus.9 Given the limited literature on LDS and neurological manifestations a review of the literature was conducted. A search (table 2) using PubMed (National Institutes of Health, National Library of Medicine, USA) identified 13 patients (eight male, five female) between 2013 and 2021. The patients were aged between 3½ and 68 years. Eight patients had TGFBR2 genetic mutation, two patients had TGFBR1, one had SMAD3 mutation and in two patients no known mutation was identified. Three patients had reported neurological symptoms, ranging from transient ischaemic attack to focal weakness. Severe headaches from reversible cerebral vasospasm reported in the 9-year-old. Headaches were also reported in the 13-year-old and 35-year-old patients, and migrainous features with headaches

### Table 2  Reported cases of Loeys-Dietz syndrome and neurological manifestations.

| Time of report | Age (years)/gender | Mutation | Presentation | Neurological manifestation | Reference |
|----------------|--------------------|----------|--------------|---------------------------|-----------|
| 6/2020         | 21/M               | TGFBR2   | Thoracic aortic aneurysm, and syringomyelia | Spinal fusion | 7         |
| 10/2019        | 68/M               | SMAD3    | Transient ischaemic attack | Asymptomatic right vertebral artery dissection | 14        |
| 10/2019        | 47/M               | TGFBR1   | Left-sided weakness | Right internal carotid artery dissection after sport activity | 14        |
| 8/2018         | 19/M               | TGFBR2   | Rupture of an ascending aortic aneurysm, craniofacial and skeletal abnormalities—initially misdiagnosed as Larsen’s syndrome | Hypotonia, sensory neural hearing loss | 28        |
| 8/2021         | 20/F               | TGFBR2   | Easy bruising and bleeding—misdiagnosed as Marfan’s syndrome | Intracranial aneurysm | 29        |
| 10/2015        | 9/M                | TGFBR2   | Severe thunderclap headaches | Reversible cerebral vasocostriction syndrome | 30        |
| 10/2017        | 36/F               | Not reported | Left eye ptosis, anosmia and shoulder pain. | Horner’s syndrome | 31        |
| 3/2011         | 13/M               | TGFBR2   | Pectus excavatum and patent ductus arteriosus closure | Chiari I malformation, and dolichocephaly | 32        |
| 4/2017         | 35/F               | TGFBR2   | Dural arteriovenous fistula | Headaches | 33        |
| 10/2013        | 66/f               | TGFBR2   | Chest pain thoracic abdominal aneurysm | Proximal paraparesis | 34        |
| 1/2014         | 14/M               | Unknown  | Myxomatous mitral/tricuspid valves with aortic root dilation | Severe proximal vasospasms | 35        |
| 12/2018        | 4/F                | TGFBR2   | Congenital heart disease | Headaches improved with β blocker | 36        |
| 12/2018        | 3.5/M              | TGFBR1   | Congenital heart disease and aortic root dilation | Headaches | 36        |

### Table 3  Paediatric cases of COVID-19 infection and febrile status epilepticus

| Time of report | Age (years)/gender | Presentation | Treatment | Outcome | Reference |
|----------------|--------------------|--------------|-----------|---------|-----------|
| 7/2020         | 11/M               | Focal status epilepticus, fever | Lorazepam | Recovered | 17        |
| 8/2020         | 2/F                | New onset febrile status epilepticus-generalised tonic-clonic seizure | Benzodiazepine, fosphenytoin | recovered | 37        |
| 7/2020         | 8/M                | Febrile status epilepticus-vomiting and head–eye deviation and left-sided shaking for 30 min | Lorazepam and levetiracetam 50 mg/kg load. Methylprednisolone 40 mg IV | Recovered | 38        |
| 10/2020        | 2/F                | Febrile status epilepticus 32 min | Levetiracetam | Recovered | 39        |
| 10/2020        | 2/F                | Status epilepticus 11 min | Levetiracetam | Recovered | 39        |
| 10/2020        | 15months/F         | Febrile status epilepticus | Phenobarbital | Recovered | 39        |
| 12/2020        | 13/F               | Fever generalised tonic-clonic status epilepticus 30 min | Lorazepam and phenytoin | Recovered | 40        |
| 2/2021         | 14/F               | PRR7Z mutation/febrile status epilepticus lasted for 6 days | Diazepam levetiracetam, midazolam, ketamine, perampanel, phenytoin propofol valproate | Died on day 135 | 41        |
| 9/2020         | 3/M                | Fever, foaming and jerking of hand and feet 30 min | Phenobarbital, levetiracetam, midazolam, IVlg | Recovered | 24        |

IVlg, intravenous immunoglobulin.
were reported in the 3½-year-old boy and 4-year-old girl. Horn-
ner’s syndrome was reported in the 36-year-old woman with LDS
syndrome. Spinal fusion was reported in the 21-year-old and
proximal paraparesis in the 66-year-old patient.
SARS-CoV-2 is the infectious agent responsible for COVID-
19. COVID-19 usually causes respiratory illness, ranging from
asymptomatic to severe acute respiratory distress syndrome.
It can cause general central nervous system manifestations,
including encephalopathy, headaches, seizures, ischaemic infarcts
and worsening of autoimmune disease.16
The proposed mechanisms by which COVID-19 causes
systemic signs include direct infection, autoimmune response,
a postinfection process, vascular processes and dysregulation of
cytokine signalling.17
Proinflammatory cytokines such as interleukin-6, interleukin-8
and interferon-γ, have been associated with febrile seizure.18
This case report of febrile status epilepticus and focal electro-
graphic seizure as the predominant presentation of COVID-19
also calls into question the neuroinvasive potential of SARS-
CoV-2. At an earlier admission the patient’s video EEG was
normal. Coronaviruses can invade cells exposed to angiotensin-
converting enzyme 2, which has been found to be expressed by
neurons and glial cells.19 In comparison with adults, neurological
manifestations of COVID-19 in the paediatric population are
not well described in the medical literature.20
Our review of literature looking for febrile status epilepticus
and COVID-19 positive infection in the paediatric population
(table 3) using PubMed (National Institutes of Health, National
Library of Medicine, USA) identified nine paediatric patients
between 2020 and 2022. These paediatric patients were diag-
nosed with febrile status epilepticus associated with COVID-19.
Patient who were afebrile and positive for COVID-19 infection or
those not in status epilepticus with COVID-19- induced fever
were not included. The patients (six female, three male) were
aged between 15 months and 14 years. Seizure duration was
reported to be between 11 min and 144 hours (6 days). Most
commonly used medication was lorazepam, midazolam and leve-
tiracetam. Eight of the nine patients recovered from COVID-19-
induced febrile status epilepticus. One patient with the PRRT2
genetic mutation died after not responding to treatment of the
refractory febrile status epilepticus with COVID-19 infection.
Kurd et al conducted a systematic retrospective chart review to
study paediatric patients between the ages of 6 months and
17 years, who presented with seizures as the main symptom of
acute COVID-19. Of 175 patients, 11 children presented with
seizures. Five presented with status epilepticus and six patients
with seizures had fever associated with COVID-19 infection.
Complete recovery was reported.21
Respiratory syncytial virus has been implicated as a cause of
febrile status epilepticus with or without respiratory involve-
ment, and it poses a higher risk of neurological deficits.22 Influen-
za virus and enterovirus are the commonly reported viruses
associated with febrile seizures,23 and it is important to recog-
nise that COVID-19 could be another risk factor for febrile seizures.24

Neurological complications such as status epilepticus are
reported in association with COVID-19 infection in up to 35% of
adults, but for children there are limited data.24
Epilepsy, febrile seizures, status epilepticus or abnormal EEG
findings have never been reported in patients with LDS.
Antony and Haneef25 performed a systematic review of the
literature to study the EEG findings in COVID-19, including
617 patients. Their study found no common EEG pattern, and
frontal lobe EEG changes were the most commonly reported.
The underlying diagnosis of LDS that is not associated with
epilepsy or febrile seizures makes this a more interesting finding,
which requires further case series to establish an association of
neurological complications with LDS.
There were focal spikes on EEG recorded in our patient,
which are associated with a heightened risk of epilepsy in future.
This case highlights the need for early recognition of this
disorder, which results in a shortened life expectancy.
Our case is unique as this is the youngest patient reported with
LDS who had a febrile seizure with a further risk of epilepsy, and
it provides an opportunity to follow-up the outcome.
As more case reports and case series are reported and patients
are diagnosed with LDS, our knowledge of the clinical course
and best management strategies will continue to evolve.
A thorough understanding of the unique anatomic findings in
patients with LDS is crucial and could be lifesaving.

Learning points
► Loes-Dietz syndrome (LDS) is a rare autosomal dominant,
multisystem disorder that was first reported in 2005.
Neurological complications have been rarely reported, but
given the arteries tortuosity, a risk of stroke, headache and
haemorrhage is present. Since most patients present with
vascular malformation complications, the early diagnosis can
be missed.
► LDS can be associated with an aggressive vascular pathology.
This case underlines the importance of recognition of this
spectrum of the syndrome. Clinical knowledge is needed to
manage this potentially catastrophic disease.
► There is no standardised clinical protocol, and clinical
knowledge will help in the early diagnosis, enabling adequate
vascular assessments and follow-up to prevent complications
such as stroke.
► Headaches and respiratory syncytial virus syndrome have
been reported with LDS, and vasoconstrictive medication is
contraindicated. Epilepsy, febrile seizures and risk of epilepsy
with abnormal EEG have not been reported with LDS.
► Febrile status epilepticus, electrographic seizures and
epileptiform activity on video EEG are associated with a
heightened risk of epilepsy in the future.
► More information on the characteristics of the clinical course
of COVID-19 is required to diagnose and manage COVID-19-
related neurological symptoms, including emergencies such
as febrile status epilepticus, especially in children; a systemic
inflammatory response due to cytokine release might be
implicated.

Twitter Sharjeel Ahmad @sharjeel__ahmad
Contributors AA wrote the initial manuscript, SA and HH made changes and
additions. SC provided the radiologic images and description. AA and HH reviewed
the video EEG and wrote the description. All authors have reviewed and approved
the final manuscript.
Funding The authors have not declared a specific grant for this research from any
funding agency in the public, commercial or not-for-profit sectors.
Competing interests None declared.
Case report

Patient consent for publication  Consent obtained from parent(s)/guardian(s)
Provenance and peer review  Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iDs
Asra Akbar http://orcid.org/0000-0002-0100-4463
Sharjeel Ahmad http://orcid.org/0000-0002-4152-2337

REFERENCES
1 Loeyls BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275–81.
2 van de Laar IMBH, van der Linde D, Oei EHG, et al. Phenotypic spectrum of the SMAD8-related aneurysms-osteoarthropathy syndrome. J Med Genet 2012;49:47–57.
3 Frischmeier-Guererro PA, Guererro AL, Oswald G, et al. Tgfb receptor mutations impose a strong predisposition for human allergic disease. Sci Transl Med 2013;5:195ra94.
4 MacCarrick G, Black JH, Bowdin S, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788–98.
5 Rodrigues VI, Elsayed S, Loeyls BL, et al. Neuroradiologic manifestations of Loeyls-Dietz syndrome type 1. AJNR Am J Neuroradiol 2009;30:1614–9.
6 Uehara M, Ito K, Kosho T, et al. Posterior spinal fusion for severe kyphoscoliosis in a Loeyls-Dietz syndrome patient with a large syringomyelia. J Clin Neurosci 2007;14:769–77.
7 Nair TV, Velmurugan A, Manjunath UD, et al. Phenotypic spectrum of the Loeyls-Dietz syndrome in the neonatal period. Pediatrics 2007;119:e1199–202.
8 Muramatsu Y, Koshii T, Magono M, et al. Progressive aortic root and pulmonary artery aneurysms in a neonate with Loeyls-Dietz syndrome type 1B. Am J Med Genet A 2010;152:417–21.
9 Laterza D, Rittell M, Zini A, et al. Novel pathogenic TGFBR1 and SMAD3 variants identified after cerebrovascular events in adult patients with Loeyls-Dietz syndrome. Eur J Med Genet 2019;62:103727.
10 Boggs JG. Mortality associated with status epilepticus. Epilepsy Curr 2004;4:25–7.
11 Luigetti M, Iorio R, Bentivoglio AR, et al. Assessment of neurological manifestations in hospitalized patients with COVID-19. Eur J Neurol 2020;27:2322–8.
12 McBee GN, Brosgol Y, Pavlakis G, et al. Encephalitis associated with COVID-19 infection in an 11-year-old child. Pediatr Neurol 2020;109:94.
13 Kim K, Kwak BO, Kwon A, et al. Analysis of plasma multiplex cytokines and increased level of IL-10 and IL-1Ra cytokines in febrile seizures. J Neuroinflammation 2017;14:1–7.
14 Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995–8.
15 Akbar A, Ahmad S. New-onset seizures as an acute presentation with atypical EEG findings in a previously healthy child with asymptomatic COVID-19 infection. Cureus 2022;10:9.
16 Kurz M, Hashayya S, Benenson S, et al. Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children. Seizure 2021;92:89–93.
17 Ude K, Kitazawa K. Febrile status epilepticus due to respiratory syncytial virus infection. Pediatr Int 2017;59:878–84.
18 Han DH, Kim SY, Lee NM, et al. Seasonal distribution of febrile seizure and the relationship with respiratory and enteric viruses in Korean children based on nationwide registry data. Seizure 2019;72:9–13.
19 Saeed A, Shoraia E. Status epilepticus as a first presentation of COVID-19 infection in a 3 years old boy; case report and review the literature. IDCases 2020;22:e00942.
20 Antony AR, Haneef Z. Systematic review of EEG findings in 617 patients diagnosed with COVID-19. Seizure 2020;83:234–41.
21 Kane BS, Shamsa K. Preventing a catastrophe: increasing awareness of Loeyls-Dietz syndrome. Tex Heart Inst J 2019;46:61–3.
22 Ueda K, Kitazawa K. Febrile status epilepticus due to respiratory syncytial virus infection. Pediatr Neurol 2020;109:94.
23 Han DH, Kim SY, Lee NM, et al. Seasonal distribution of febrile seizure and the relationship with respiratory and enteric viruses in Korean children based on nationwide registry data. Seizure 2019;72:9–13.
24 Rahme RJ, Adel IG, Bendok BR, et al. Association of intracranial aneurysm and Loeyls-Dietz syndrome: case illustration, management, and literature review. Neurosurgery 2011;69:E488–93.
25 Akarawan’Y, Inaba Y, Hachiya A, et al. Reversible cerebral vasconstriction syndrome and posterior reversible encephalopathy syndrome in a 19-year-old male: a case report. BMC Med Genet 2018;19:1–7.
26 Kane BS, Shamsa K. Preventing a catastrophe: increasing awareness of Loeyls-Dietz syndrome. Am J Med Genet A 2015;167:2435–9.
27 Cho S-M, Di Lorenzo R, Mathew J, et al. Teaching NeuroImages: Rare cause of Horner syndrome in Loeyls-Dietz syndrome. Neurology 2017;89:174–5.
28 Suarez B, Caldera A, Castillo M. Imaging and clinical features in a child with Loeyls-Dietz Syndrome. A case report. Interv Neuroradiol 2011;17:9–11.
29 Weber W, Kis B, Esser J, et al. Endovascular treatment of a dural arteriovenous fistula of the transverse sinus by recanalisation, angioplasty and stent deployment. A case report and follow-up. Interv Neuroradiol 2003;9:65–9.
30 Goshgarian C, Lupo A, Salazar R. Proximal pauparasis due to aortic dissection extending into bilateral carotid arteries in a patient with Loeyls-Dietz syndrome. J Clin Neurosci 2013;20:1790–2.
31 Kellner CP, Sussman ES, Donaldson C, et al. Cerebral arterial angioiplasty in a patient with Loeys-Dietz syndrome. J Neurointerv Surg 2015;7:e2.
32 Samanta D. Headaches in Loeyls-Dietz syndrome. J Child Neurol 2019;34:144–7.
33 Chegondi M, Kothari H, Chacham S, et al. Coronavirus disease 2019 (COVID-19) associated with febrile status epilepticus in a child. Cureus 2020;12:e9840.
34 Farley M, Zuberi J. COVID-19 precipitating status epilepticus in a pediatric patient. Am J Case Rep 2020;21:e295767–1.
35 Sandoval F, Julio K, Méndez G, et al. Neurologic features associated with SARS-CoV-2 infection in children: a case series report. J Child Neurol 2021;36:853–66.
36 Natarajan S, Ganesh R, Palaniappan N, et al. SARS-CoV-2 encephalitis in an adolescent girl. Indian Pediatr 2020;57:1186.
37 Vergara D, Rubilar C, Witting S, et al. Super-refractory status epilepticus related to COVID-19 in a paediatric patient with PRRT2 mutation. Epileptic Disord 2021;23:951–3.