

# Ictus emeticus presenting as an unusual seizure type in chromosome 22q11.2 deletion syndrome

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**ABSTRACT** – We present a case study of a patient with chromosome 22q11.2 deletion syndrome presenting with ictus emeticus, together with a review of the relevant literature. The patient developed generalized tonic-clonic seizures at 3 months old, and seizures eventually remitted after calcium therapy. He then experienced vigorous vomiting that occurred during sleep, with glassy eyes and legs flexion. Video-EEG recordings exhibited a switch in background activity from organized reactivity during normal sleep to left lateralized temporal delta activity, which was bilaterally synchronized during an emetic attack. The ictal vomiting ceased following management with oxcarbazepine, high-dose phenobarbital, and a ketogenic diet. The unique seizure type and rare ictal EEG findings are the first reported in a child with chromosome 22q11.2 deletion syndrome. This case highlights that ictus emeticus without detectable epileptic discharge on EEG is one potential epileptic presentation in this genetic syndrome. [*Published with video sequence on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)*]

**Key words:** chromosome 22q11.2 deletion syndrome, ictus emeticus, bilateral polymicrogyria



VIDEO ONLINE

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Chromosome 22q11.2 deletion syndrome (22q11.2DS) is the most frequent interstitial deletion syndrome in humans. It has an incidence of 1 in 4,000 live births, with 90% of cases arising *de novo*

(Scambler, 2000). Highly variable phenotypes of 22q11.2DS can manifest in various organs, including facial dysmorphism, thymic hypoplasia, velopharyngeal insufficiency, congenital heart disease (CHD),

and psychiatric illness. This phenotypic variability results from breakpoint heterogeneity, as well as familial and environmental factors (Karayiorgou *et al.*, 2010). Previous studies have reported an increased risk of provoked and unprovoked seizures in 22q11.2DS patients. The prevalence of epilepsy in 22q11.2DS patients ranges from 15.2% (Kim *et al.*, 2016) to 21% (Ryan *et al.*, 1997). Furthermore, at least 10% of 22q11.2DS patients experience hypocalcaemic seizures, which rarely present after the neonatal period. Structural brain abnormalities, such as polymicrogyria (PMG), cerebellar hypoplasia, and callosum agenesis (Robin *et al.*, 2006), can contribute to the occurrence of seizures. Of these, bilateral PMG is the most commonly reported in 22q11.2DS, causing more frequent seizures than in those without PMG (47% vs 21%) (Robin *et al.*, 2006). Previous studies report a prevalence of genetic epilepsy in 22q11.2DS between 4.8% and 8.3% (Kao *et al.*, 2004). Most patients with genetic epilepsy present with generalized seizures, including myoclonic epilepsy, which is associated with both juvenile myoclonic epilepsy and 22q11.2DS (Lemke *et al.*, 2009).

Seizures with ictus emeticus are relatively frequent in children with epilepsy. However, such seizures have never been described in patients with 22q11.2DS. Here, we present a 3-year-old boy with 22q11.2DS, presenting with cyclic and intractable vomiting that was successfully treated as ictus emeticus. This case provides additional clinical insights for a relatively rare condition in 22q11.2DS patients.

## Case history

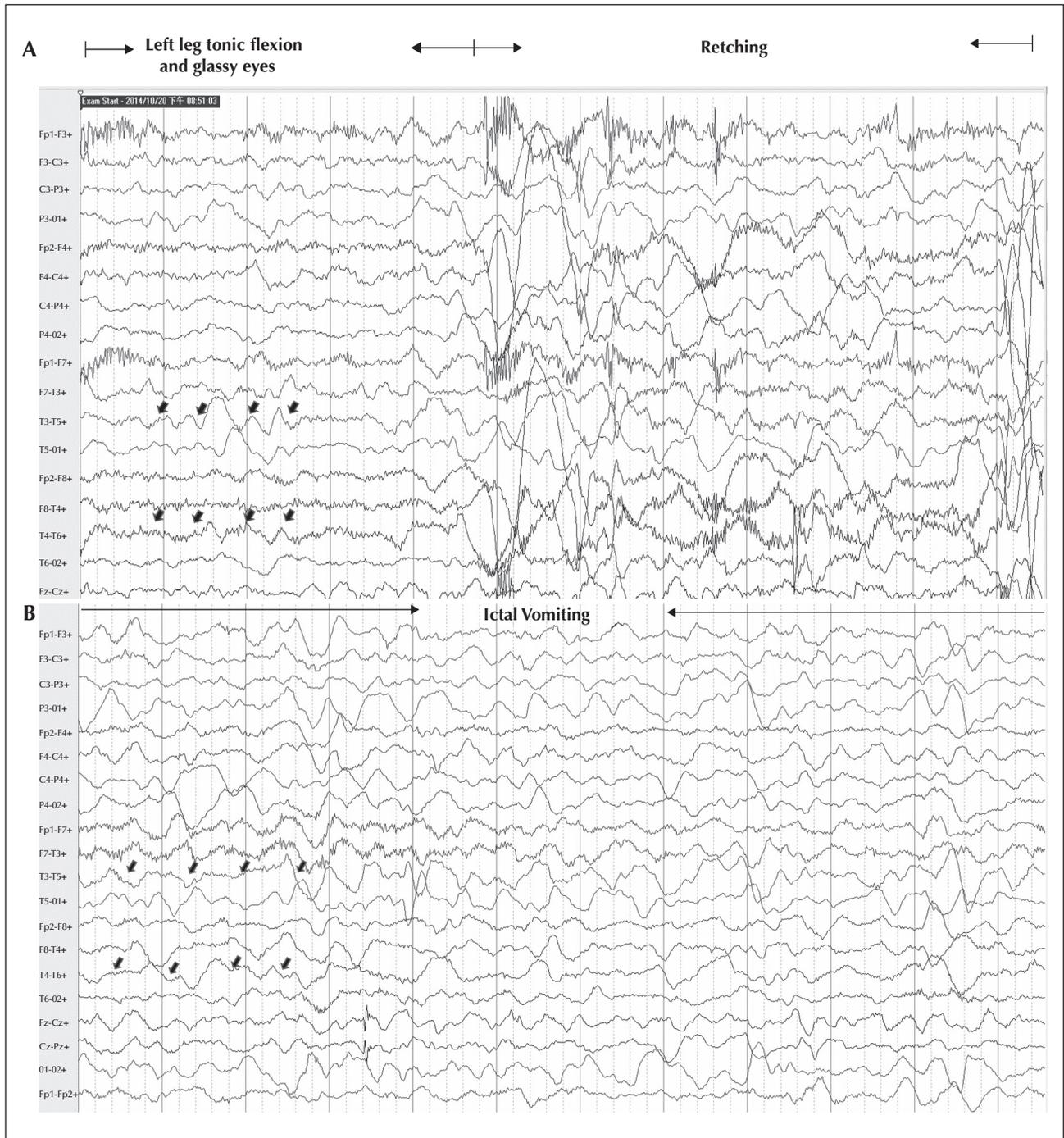
The patient was a boy, 3 years and 2 months old. He was right-handed and the first child of healthy parents with an uneventful family medical history. The pregnancy proceeded without complications, and he was born at full term, weighing 3,120 g. He was admitted to a paediatric intensive care unit following hypocalcaemic convulsions at 3 months old, with serum calcium levels as low as 5.5 mg/dl. The hypocalcaemia was rapidly corrected within five days. In addition to hypocalcaemia, the patient also exhibited other unusual clinical features, including blonde hair (an unusual feature in Asian children), and congenital heart disease with an atrial septum defect. A clinical diagnosis of chromosome 22q11.2DS (OMIM 192430) was later confirmed using a FISH probe.

At one year old, the patient began to experience vigorous vomiting that was sufficiently severe to result in upper gastrointestinal (GI) bleeding. A series of tests, including an upper GI series, endoscopic examination with mucosal membrane biopsy, and an abdominal CT were performed. However, the results were unremarkable. The Multiple Allergen Simultaneous Test

assay and serum total-IgE were normal. We evaluated the amino acid profile, urine organic acidopathy, and plasma L-carnitine levels, but the results were within normal limits. We prescribed steroids, antacids, H2 receptor antagonists, a proton pump inhibitor, and a hydrolysed formula, but the vomiting persisted. Emetic attacks were usually long, lasting for two weeks with peak frequency reaching 175 episodes per day. This was followed by five days free of symptoms before another vomiting episode began.

The patient also displayed gross motor and language development delays. Additionally, he had severe growth retardation caused by periodic vomiting, weighing only 6.5 kg at one year old. We observed that when the patient began to vomit, he appeared subdued and dazed, and lost the ability to make sound. The patient always flexed his legs during emesis. Video-EEG recordings exhibited asymmetric and discontinued delta rhythms originating from the left posterior temporal region (T3, T5) when the boy showed right leg flexion with retching. After a few minutes, the EEG background became synchronized bilaterally with posterior temporal lobe delta rhythms as he began vomiting (see *video sequence, figure 1*). 3DT1 brain MRI revealed bilateral polymicrogyria (*figure 2A*). Additionally, there was reduced white matter volume, and hyperintense lesions appeared in T2-weighted images, indicating heterotopia. Interictal FDG positron emission tomography (FDG-PET) investigations of glucose metabolism revealed diffuse decreases in FDG uptake, especially in the right parietal area (*figure 2B*). Under the impression that these features represented ictal vomiting, we started anticonvulsant therapy. The frequency of emesis significantly decreased with a high dose of phenobarbital (PHB) (10 mg/kg/day) (*figure 2A*). However, emesis did not completely remit following administration of PHB with adjunctive anticonvulsants. We initiated ketogenic diet therapy in May 2014. Following this, we observed a substantial increase in the symptom-free intervals (*figure 2C*). In November 2014, the patient's family sought a second opinion at another medical centre. Their suggestion to cease ketogenic diet therapy demonstrated the effectiveness of this therapy for the patient, as the symptom-free interval became shorter following cessation (*figure 2D; arrow*). Therefore, ketogenic diet therapy was reinitiated in January 2015, and emesis has been in remission since February 2015. Hypocalcaemia may result in vomiting in patients with DiGeorge syndrome, however, the frequency of emesis did not correlate with serum calcium levels (see *supplementary figure*).

During this patient's regular outpatient visits, he has remained seizure-free for 10 months and his body weight is now comparable to that of his peers.

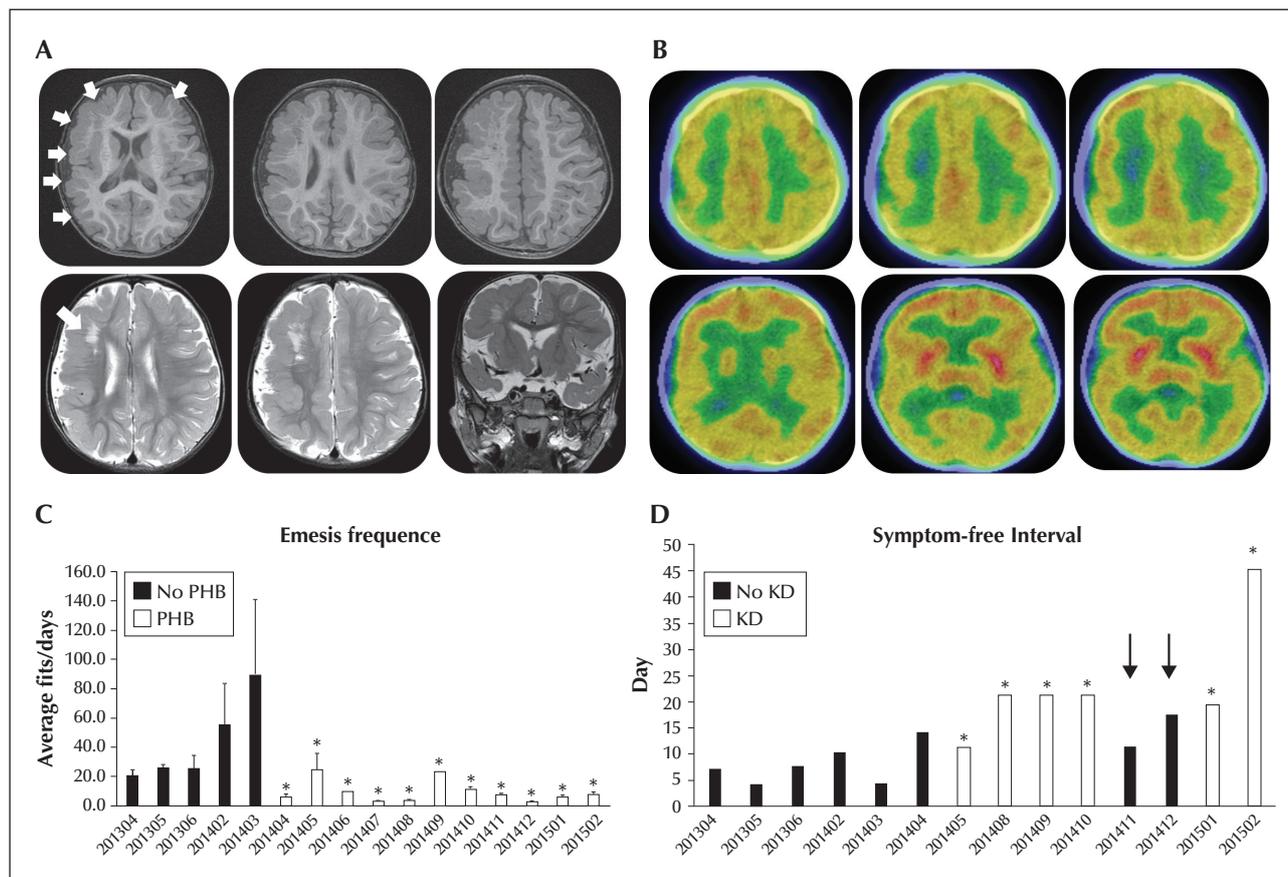


**Figure 1.** The EEG background showed asymmetric and discontinued delta rhythm across the left posterior temporal lobe during left leg flexion and retching (A). Ictal EEG documented symmetric and synchronized delta rhythm over posterior temporal regions during vigorous vomiting (B).

## Discussion

22q11.2DS is a common microdeletion syndrome affecting over 1 in 5,000 children. It is reported among several overlapping phenotypes, including

velocardiofacial syndrome, DiGeorge syndrome, and conotruncal heart malformation. The clinical presentation of 22q11.2DS in paediatric patients and neonates is highly variable. The manifestations can involve multiple organ systems and vary in severity. Commonly



**Figure 2.** Axial T1 3D FSPGR demonstrated right hemisphere polymicrogyria (PMG) with a flattened cortical surface and excessive surface convolutions (A: upper panels; white arrows). T2-weighted images revealed heterotopic neurons in the right frontal white matter zone (A: lower panels; white arrows). Interictal FDG-PET exhibited diffuse hypometabolism, especially in the right parietal region (B). Emetic frequency significantly decreased after phenobarbital administration in April 2014 (C: blank bars), and symptom-free intervals were prolonged in conjunction with ketogenic diet therapy (D: black bars). When the patient discontinued ketogenic diet therapy between November and December 2015, the symptom-free interval was significantly shortened (D: black arrows). \* $P < 0.05$ .

associated symptoms include behavioural problems, developmental and learning disabilities, conotruncal cardiac anomalies, palatal defects, hypernasal speech, immunodeficiency, hypocalcaemia, and characteristic facial features (McDonald-McGinn and Sullivan, 2011). GI alterations are often reported in patients with 22q11.2DS. The most common comorbidities are gastroesophageal reflux disease, oesophagitis, and chronic constipation. Patients with feeding difficulties caused by dysmotility in the pharyngoesophageal area characteristically have suction/deglutition/breathing reflex incoordination, which results in slow feeding and episodes of regurgitation (Rommel *et al.*, 1999). Some anatomical GI abnormalities result in vomiting, including oesophageal atresia, jejunal atresia, and intestinal malrotation, and these are also reported in patients with 22q11.2DS (Ryan *et al.*, 1997). However, our patient usually developed forceful emesis while sleeping, but not during meals, and detailed laboratory

examinations did not provide evidence of GI alterations or anatomical abnormalities.

In this patient, emesis with altered consciousness and limb hypertonia indicates the possibility of convulsion. We attributed the vigorous vomiting of the patient to ictus emeticus (ictal vomiting) based on his clinical manifestations and favourable response to phenobarbital and ketogenic diet therapy. Several brain malformations have been described in association with 22q11.2DS, such as polymicrogyria (PMG), cerebellar hypoplasia, mega cisterna magna, and corpus callosum agenesis (Robin *et al.*, 2006). Polymicrogyria is the most frequently reported brain malformation in patients with 22q11.2DS (Cramer *et al.*, 1996). In 22q11.2DS, PMG seems to mainly be located in the perisylvian area and is frequently asymmetric, occurring predominantly in the right hemisphere. Seizure disorders are a neurological feature of PMG (Robin *et al.*, 2006). Seizures usually begin between ages four

**Table 1.** Summary of seizure types in patients with 22q11.2DS.

Authors	Study design	Year	no. of cases	Prevalence of seizure (no. cases with seizure) (%)	Seizure aetiology (% cases with seizure)	Seizure classification (% cases with seizure)
Kao <i>et al.</i>	Retrospective study	2004	383	8 (21%)	Provoked <sup>a</sup> (n=54, 68%) Hypocalcaemia (n=35, 43%) Post-operative HIE (n=24, 30%) Fever seizure (n=19, 23%) Unprovoked (n=27, 32%)	Partial seizure (n=19, 23%) Generalized seizure (n=8, 8.6%)
Ryan <i>et al.</i>	Cohort	1997	558	62 (21%)	Hypocalcaemia (68%) Febrile seizure (9.6%) Structural malformations (32%) Hyponatraemia (1.6%) Unspecified (17.7%)	NA
Hiéronimus <i>et al.</i>	Cohort	2006	19	3 (15.8%)	Hypocalcaemia (100%)	Generalized seizure (100%)
Kim <i>et al.</i>	Cohort	2016	145	22 (15.2%)	Genetic epilepsy (54.5%) Structural epilepsy (45.5%)	Generalized seizure (73%) Focal clonic seizure (18%) Myoclonic seizure (9%)
Roubertie <i>et al.</i>	Case report	2001	3	NA	Hypocalcaemia (n=1) Unprovoked (n=1)	Focal seizure Atypical seizure
Coppola <i>et al.</i>	Case report	2001	1	NA	Unprovoked	Benign idiopathic partial epilepsy
Lemke <i>et al.</i>	Case report	2009	1	NA	Unprovoked	Juvenile myoclonic epilepsy

<sup>a</sup>many patients had more than one seizure type

and 12, and are ineffectively controlled in approximately 65% of patients with PMG. Kao *et al.* reported an increased prevalence of unprovoked seizures in individuals with 22q11.2DS and suggested that generalized epilepsy may be a primary manifestation of the disorder (Kao *et al.*, 2004). Other commonly reported seizure types include atypical absence, tonic seizures, atonic drop attacks, and tonic-clonic seizures, which often manifest with similar symptoms to Lennox-Gastaut syndrome (Roubertie *et al.*, 2001). A minority of patients (approximately 25%) have partial seizures, and juvenile myoclonic epilepsy has been also reported to be related to 22q11.2DS (Lemke *et al.*, 2009). All seizure types reported in 22q11.2DS from our literature review are summarised in *table 1*.

Our patient exhibited ictal vomiting, which has not previously been reported in patients with 22q11.2DS. The possible mechanism of ictal vomiting in such patients involves the spread of abnormal electrical activity through descending insular or limbic circuits (Devinsky *et al.*, 1995). However, this is also considered a localizing sign in patients with partial seizures

originating from the left temporal region, which is usually the language-dominant hemisphere (Fiol *et al.*, 1988). In cases of childhood abdominal epilepsy, a seizure may be associated with bi-hemispheric slowing, with delta and theta bursts and runs of high-voltage 1-2-Hz activity over the right temporal area (Mitchell *et al.*, 1983). Although evidence indicates that epileptic vomiting can arise not only from the dominant, but also the non-dominant hemisphere (Devinsky *et al.*, 1995), ictal EEG in our patient showed a slowing delta wave over the left temporal area associated with loss of speaking ability. This supported our conclusion that his seizures originated from the left temporal area, which is generally the language-dominant hemisphere.

In our patient, the EEG epileptogenic zone did not correspond to brain structural malformations. Thus, we attempted to explain the discrepancy by reviewing the literature on FDG-PET presentations. Interictal FDG-PET has been demonstrated as a useful and sensitive imaging method for delineating lesions of focal cortical dysgenesis in infants. FDG-PET has shown

interictal cortical hypometabolism at the focus of a lesion to be present in 85-90% of patients with focal cortical dysplasia. FDG-PET is particularly useful for delineating cortical abnormalities (Kim *et al.*, 2000). Although MRI indicated cortical malformation in the right hemisphere of our patient, interictal FDG-PET revealed bilateral hypometabolism. This possibly indicated bilateral PMG, which is indicative of brain malformation in patients with 22q11.2DS (Castro *et al.*, 2011).

## Conclusion

Bilateral PMG is an indicative feature of CNS malformation in 22q11.2DS, which may precipitate seizures. Various seizure types have been reported in patients with 22q11.2DS. However, this is the first study to report ictus emeticus in a patient with 22q11.2DS. Ictal EEG revealed discontinuation of delta slow activity originating from the left temporal region. This is the language dominant hemisphere and may correspond to his loss of speech during seizures. Paediatric neurologists should be aware of potential ictus emeticus in patients with 22q11.2DS who present with cyclic vomiting. □

### Supplementary data.

Summary didactic slides and supplementary figure are available on the [www.epilepticdisorders.com](http://www.epilepticdisorders.com) website.

### Disclosures.

No authors have any conflict of interest to disclose.

### Legend for video sequence

At 08:53:09, the patient is retching with tonic spasms. EEG recordings at this time revealed discontinued and unsynchronized slow waves across the left temporal area (T3, T5). When retching developed into forced emesis, the slow waves evolved into bilateral synchronization across temporal areas.

#### Key words for video research on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

*Phenomenology:* ictus emeticus  
*Localization:* left temporal region  
*Syndrome:* chromosome 22q11.2 deletion  
*Aetiology:* genetic epilepsy

## References

Castro A, Rodrigues N, Pereira M, *et al.* Bilateral polymicrogyria: always think in chromosome 22q11.2 deletion syndromes. *BMJ Case Rep* 2011; doi: 10.1136/bcr.09.2011.4860.

Coppola G, Sciscio N, Russo F, Caliendo G, Pascotto A. Benign idiopathic partial seizures in the velocardiofacial syndrome: report of two cases. *Am J Med Genet* 2001; 103(2): 172-5.

Cramer SC, Schaefer PW, Krishnamoorthy KS. Microgyria in the distribution of the middle cerebral artery in a patient with DiGeorge syndrome. *J Child Neurol* 1996; 11: 494-7.

Devinsky O, Frasca J, Pacia SV, *et al.* Ictus emeticus: further evidence of nondominant temporal involvement. *Neurology* 1995; 45: 1158-60.

Fiol ME, Leppik IE, Mireles R, *et al.* Ictus emeticus and the insular cortex. *Epilepsy Res* 1988; 2: 127-31.

Hiéronimus S, Bec-Roche M, Pedetour F, *et al.* The spectrum of parathyroid gland dysfunction associated with the microdeletion 22q11. *Eur J Endocrinol* 2006; 155(1): 47-52.

Kao A, Mariani J, McDonald-McGinn DM, *et al.* Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. *Am J Med Genet A* 2004; 129a: 29-34.

Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat Rev Neurosci* 2010; 11: 402-16.

Kim SK, Na DG, Byun HS, *et al.* Focal cortical dysplasia: comparison of MRI and FDG-PET. *J Comput Assist Tomogr* 2000; 24: 296-302.

Kim EH, Yum MS, Lee BH, *et al.* Epilepsy and other neuropsychiatric manifestations in children and adolescents with 22q11.2 deletion syndrome. *J Clin Neurol* 2016; 12: 85-92.

Lemke JR, Beck-Wodl S, Zankl A, *et al.* Juvenile myoclonic epilepsy with photosensitivity in a female with velocardiofacial syndrome (del(22)(q11. 2))-causal relationship or coincidence? *Seizure* 2009; 18: 660-3.

McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Medicine (Baltimore)* 2011; 90: 1-18.

Mitchell WG, Greenwood RS, Messenheimer JA. Abdominal epilepsy. Cyclic vomiting as the major symptom of simple partial seizures. *Arch Neurol* 1983; 40: 251-2.

Robin NH, Taylor CJ, McDonald-McGinn DM, *et al.* Polymicrogyria and deletion 22q11.2 syndrome: window to the etiology of a common cortical malformation. *Am J Med Genet A* 2006; 140: 2416-25.

Rommel N, Vantrappen G, Swillen A, *et al.* Retrospective analysis of feeding and speech disorders in 50 patients with velo-cardio-facial syndrome. *Genet Couns* 1999; 10: 71-8.

Roubertie A, Semprino M, Chaze AM, *et al.* Neurological presentation of three patients with 22q11 deletion (CATCH 22 syndrome). *Brain Dev* 2001; 23: 810-4.

Ryan AK, Goodship JA, Wilson DI, *et al.* Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 1997; 34: 798-804.

Scambler PJ. The 22q11 deletion syndromes. *Hum Mol Genet* 2000; 9: 2421-6.