

Cyclic Vomiting Syndrome in a Baby with 22q 11 Deletion Syndrome

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Abstract

Cyclic vomiting syndrome (CVS) is an episodic disorder that may be associated with migraine. It is characterized by recurrent, stereotypic episodes of vomiting and nausea separated by intervals of comparative wellness. We report the first pediatric case of 22q 11 deletion syndrome (22q11DS) and CVS.

Keywords: Cyclic Vomiting Syndrome (CVS); 22q 11 Deletion Syndrome (22q11DS)

Introduction

22q 11 deletion syndrome (22q11DS; Online Mendelian inheritance in man #192430) also known as velocardiofacial or DiGeorge syndrome, is a genetic disorder resulting from a hemizygous microdeletion of the long arm of chromosome 22. It has an estimated prevalence of 1 out of 4000 live births and results in a heterogeneous clinical presentation that is irrespective of deletion size and can be associated with multi-organ dysfunction. Its physical manifestations frequently include cleft palate, hypocalcemia, cardiac defects and immune dysfunction [1,2].

Gastrointestinal alterations, including feeding disorders and congenital abnormalities, are often reported [3]. The most frequent congenital abnormalities include esophageal atresia, jejunal atresia, umbilical hernia, diaphragmatic herniation, intestinal malrotation, congenital megacolon, anorectal malformations (atresia, anterior displacement).

22q11.2 DS is also associated with strikingly elevated risk for neuropsychiatric illness, particularly psychosis [4]. Moreover, nonpsychotic psychiatric disorders and behavioral abnormalities are present from early childhood [5]. Several genes included in the deleted region are highly expressed in the brain and affect early neuronal migration and cortical development [6].

Cyclic vomiting syndrome (CVS) is an idiopathic chronic disorder characterized by recurrent episodes of vomiting and nausea separated by symptom-free intervals [7].

The exact prevalence of cyclic vomiting syndrome is unknown; estimates range from 4 to 2,000 per 100,000 children. In the International Classification of Headache Disorders III beta version, it is included among the episodic symptoms which may be associated with migraine [8]. Although the pattern of vomiting episodes is variable among patients, hyperemesis phase usually starts in the early morning, lasts from 24 to 48 hours, and is characterized by intense nausea and repeated vomiting. About one-half of children have attacks at regular intervals (from two to four weeks). A prodromal phase of pallor, anorexia, lethargy, abdominal pain or autonomic symptoms (salivations) frequently precedes the vomiting. During the interictal phase patients are relatively asymptomatic.

Case Presentation

Here we report the case of a female baby with a diagnosis of 22q11 DS and a clinical history of CVS responding to treatment with flunarizine.

Our baby was admitted for the first time at our hospital at the age

of 15 months, in good general condition (weight 10 kg, length 86 cm, 3rd pc for age). She is the second daughter of Colombian unrelated parents, born at term after an uncomplicated pregnancy, with a neonatal weight of 2,650 kg. At birth, facial dysmorphisms and a cleft palate was noted. An echocardiography revealed the presence of intraventricular septal defect and left ventricular hypertrophy. Multiplex ligation-dependent probe amplification (MPLA) confirmed the complete deletions of A, B and C regions of cluster 22q11.12 diagnostic for 22q11DS. Her medical history was characterized by the recurrence of vomiting since the first months of life, usually anticipated by a prodromal period, lasting 3-6 hours before the onset and characterized by pallor, anorexia, salivations and photophobia. She underwent multiple hospital admissions due to vomiting. All causes for vomiting (anatomic, infective and metabolic disorders) were excluded, in particular metabolic survey, including analysis of urinary organic acids, and a blood amino acid assay found nothing specific during both acute phase and interictal period; electroencephalography never showed epileptic activity. At the age of 6 months the duration of episodes was so long (5-7 days), so severe (> 50 episodes per day) and with an interval free of symptoms so short (2-3 days) that nutrition support was started with total parenteral nutrition. Her mother suffered from recurrent attacks of headache with the clinical characteristics of migraine without aura.

Diagnosis and Prophylactic Measures

A diagnosis of CVS was suspected and prophylactic treatments with L-carnitine, cyproheptadine and erythromycin were attempted without improvement. At the age of 15 months, a trial with flunarizine per OS was started (2 mg/die - 0.2 mg/kg/die).

The number of episodes of vomiting per hour progressively reduced, while the interval between attacks increased. Parenteral nutrition was stopped, and usual diet was restarted.

Feeding disorders, mostly due to dysmotility in the pharyngoesophageal area, are often reported in patients with 22q11DS [3]. However, as far as we know, our patient is the first pediatric case of CVS in 22q11DS.

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Discussion

CVS is a debilitating disorder of the brain–gut neuroendocrine system. Although the etiology of CVS remains unknown, it's considered as part of the migrainous syndrome and an association between CVS and maternal migraine has been described [9,10]. An association with other genetic syndromes was recently described in literature [11,12]. In some patients, ornithine, citrulline and arginine without ammonia were abnormal at times of vomiting, which correlate with the urea cycle and may suggest a pathogenic role. In fact, as in urea cycle disorders, dextrose-containing intravenous fluid therapy helped in effectively managing the acute phase of cyclic vomiting in these patients. Indeed, other patients showed normal amino acids profiles so they cannot completely exclude the possibility of coincidental cyclic vomiting.

Since there are no specific diagnostic tests, CVS often undergo extensive evaluation for alternative causes of their symptoms and the diagnosis of CVS is based on the exclusion of other disorders which could cause vomiting. For this reason, there is usually a long interval between the onset of symptoms and diagnosis, as occurred in our patient.

Treatment and Medications

No specific therapy is available, and treatments consist to a supportive care during severe attacks and include intravenous fluid replacement with electrolyte solutions and anti-emetics. There is no evidence for the efficacy of different anti emetics, and smooth-muscle relaxants, H1 histamine 5-HT receptor antagonists and ondansetron are alternatively used in clinical practice. Management is also aimed to reduce the frequency and severity of the episodes: CVS may respond to migraine-directed prophylaxis (beta-blockers, amitriptyline, and cyproheptadine) [7,13,14]. Currently, flunarizine have shown best evidence of efficacy for migraine prophylaxis in children and adolescents.

Flunarizine is a non-selective calcium antagonist that has an established efficacy in migraine prophylaxis and was successfully used in a small cohort of pediatric patients with CVS [15,16]. Although the efficacy has only been shown in small series, the long half-life with once a day dosing and the good safety profile makes it an attractive therapy for pediatric population. In our patient, flunarizine proved highly effective in improving her quality of life.

Conclusion

In conclusion, CVS is a syndrome still insufficiently known by pediatricians, therefore it is often misdiagnosed. As far as we know, our baby is the first patient with 22qDS presenting with CVS. Since no

similar case has been reported, further observations may clarify if this association is more than casual.

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