Electroclinical features of benign infantile seizures with mild gastroenteritis

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ABSTRACT – The purpose of this study was to analyze the electroclinical features of patients with benign infantile seizures with mild gastroenteritis and demonstrate the benign nature of this entity. From 30 patients who were included in the study, five were excluded (two with developmental delay, one with microcephaly and two lost during follow-up). Twenty-five patients who fulfilled the diagnostic criteria for benign infantile seizures with mild gastroenteritis were assessed and followed at the Pediatric Department, Armed Forces Hospital, Southern Region, Khamis Mushayt, Saudi Arabia, between January 2004 and January 2009. The median age at presentation was 10.4 months. Of the infants, 14 were females and 11 were males. Seizures were focal tonic or clonic in eight (32%) patients, focal with secondary generalisation in three (12%), generalised tonic-clonic in nine (36%) and consisted of staring only with no motor components in five (20%). Interictal electroencephalograms and brain imaging were normal for all patients. No patient required treatment with antiepileptic drugs. All the patients were found to have normal psychomotor development and neurological examination after a follow-up period of between 15 and 56 months. The limitations of this study are the relatively small sample size, relatively short study period and the fact that the study was conducted in a tertiary referral hospital. The prevalence of this entity may be more common at the level of primary health centres. Increasing the awareness of clinicians regarding the existence of this syndrome and its benign nature in children will limit unnecessary investigations. [Published with video sequences]

Key words: infantile seizures, mild gastroenteritis, rotavirus

Benign infantile seizures (BIS) were first described by Fukuyama more than 45 years ago (1963). The two types (familial and non-familial) are now considered as one syndrome, which is age-related, appearing at 2-24 months of age (Engel, 2006; Caraballo et al., 2003; Saadeldin et al., 2010). Gastroenteritis (GE) is generally defined as a decrease in the consistency of stools and/or an increase in the frequency of evacuations (≥3 in 24 hours), with or without fever or vomiting. Mild GE is defined as diarrhoea and/or vomiting without clinical signs of dehydration or electrolyte disturbance. Benign infantile seizures
Benign infantile seizures with mild gastroenteritis

with mild gastroenteritis (BISwG) were described in Japan almost 30 years ago by Morooka (1982). More than 60 reports and 10 series have followed in other parts of Asia and the rest of the world (Caraballo et al., 2003; Contino et al., 1994; Wong, 2001; Lynch et al., 2001), however, to the best of my knowledge, no cases have been reported in Saudi Arabia or other Arab countries.

Benign infantile seizures with mild gastroenteritis is characterized by the following criteria:

- occurrence in infants aged between 4-30 months (average 17 months);
- infants with normal psychomotor development and neurological examination;
- seizures may be focal or generalised;
- seizures are usually brief and repetitive and in clusters but can be isolated;
- associated with mild GE;
- associated with low grade (<38°C) or absent fever;
- not associated with electrolyte derangement or hypoglycaemia, normal CSF;
- normal interictal electroencephalography (EEG) and brain imaging;
- benign course (Uemura et al., 2002; Kawano et al., 2007; Komori et al., 1995; Caraballo et al., 2009).

The aim of this study is to discuss electroclinical features and other data with published reports of BISwG, increase the awareness of the benign nature of the disorder amongst paediatricians and paediatric neurologists and demonstrate for the first time the presence of BISwG in Saudi Arabia.

Methods

Patients

A case series was conducted with 25 infants diagnosed with BISwG. The patients were seen at the Armed Forces Hospital, Southern Region (AFHSR), Pediatric Department, Saudi Arabia between January 2004 and January 2009. The AFHSR is a tertiary referral centre in the South of Saudi Arabia with a catchment population of approximately 1,100,000.

Inclusion criteria included: (1) infants between 4-30 months of age; (2) normal psychomotor development and neurological examination before and after the onset of seizures; (3) seizures occurring during a mild course of GE; and (4) normal interictal EEG and brain imaging. Exclusion criteria included: (1) infants younger than four months or older than 30 months; (2) psychomotor delay and abnormal neurological examination before and/or after the onset of seizures; (3) personal history of febrile and/or afebrile seizures; (4) patients with moderate or severe GE and/or associated electrolyte imbalance, fever greater than 38°C or hypoglycaemia; (5) abnormal CSF study (if performed); (6) positive stool culture for bacteria; and (7) abnormal interictal EEG and brain imaging.

Clinical investigation

Thirty infants with BISwG who were admitted to the paediatric general ward were analyzed for the following characteristics: age at onset, clinical features, frequency and type of seizures associated with GE, and interval between GE and seizures. As most of the seizures occurred during hospitalization, they were witnessed by nurses, paediatricians, and/or a paediatric neurologist (IYS). At the patients’ homes, video clips of clusters of seizures were recorded on a mobile telephone by the parents of two patients and examined by a paediatric neurologist (IYS). Three patients developed some of their seizures during their stay in the paediatric ward which were witnessed by expert paediatricians and/or a paediatric neurologist (IYS). A focal seizure was defined when the seizures involved a localized part of the body and generalised seizures when bilateral symmetrical motor manifestations were present. Patients who presented only staring, unresponsiveness and motor arrest were considered as having focal seizures. Personal and family history, consanguinity, developmental history, and physical and neurological examination were obtained. Full blood count, serum electrolytes, serum renal and liver function tests, capillary blood gases, blood sugar, and urinalysis were investigated. Rotavirus antigen was examined from a stool sample for all patients using the following commercially available rapid latex agglutination kits: Remel Rotavirus Latex Test (Remel Europe Ltd, Kent, UK) and Virotect Rota (Omega Diagnostics Ltd, Scotland, UK). All stool specimens were sent for bacterial culture. CSF study was done when clinically indicated. Interictal EEG during sleep and upon awakening (and for one patient an ictal EEG) were performed using the international 10-20 system for all patients. A CT and/or MRI brain study was performed for all patients. The patients were followed at paediatric neurology clinics for up to 56 months by a paediatric neurologist (IYS).

Results

Thirty patients who presented with seizures associated with mild GE between 4-30 months of age were studied (figure 1). Three patients were excluded from the beginning (two with developmental delay and one with microcephaly) and another two patients were lost during follow-up. From the remaining 25 patients, 14 (56%) were females and 11 (44%) were males. The median age at presentation was 10.4 months.
Infants (4 m-30 m) presented with seizures associated with GE. n=30

Excluded
Microcephaly =1
Developmental delay=2

BISwG n=27

15 -56 months follow-up

Excluded n=2 Lost during follow-up

BISwG n=25
Female:14
Male:11

Figure 1. Benign infantile seizures with mild gastroenteritis; follow-up of 25 patients.
BISwG: benign infantile seizures with mild gastroenteritis; m: months; n: number; GE: gastroenteritis.

The patients were followed for 15-56 months (median: 35.6 months) and at last follow-up visit they all showed normal psychomotor development and neurological examination.

Seizures

As shown in table 1, all patients developed seizures during the first five days of GE. No patient developed a seizure before the onset of diarrhoea and/or vomiting. Seizures were isolated or occurred in clusters ranging from two to four clusters during the first five days of GE. Each cluster was composed of two to three episodes. Six patients developed two clusters (24%), five had three clusters (20%) and two had four clusters (8%). Isolated seizures (one episode only) were observed in 12 patients (48%). The interval between GE onset and appearance of the first seizures ranged from the same day to the fifth day (mean: 2.5 days). Seizures were focal tonic or clonic in eight patients (32%), focal with secondary generalisation in three (12%), generalised tonic-clonic seizures (GTCS) in nine (36%) and consisted of staring only with no motor components (see video sequence) in five (20%). The duration of seizures ranged from 25 seconds to two minutes. No patient needed antiepileptic treatment. During follow-up, all infants had normal milestones and there was no recurrence of seizures.
Personal history
Two patients (one girl and one boy) were delivered by Caesarian section and required admission to hospital for a few days. Two infants (Patients 3 and 12) were admitted at the ages of two and five months, respectively, due to viral bronchiolitis. One infant had a history of neonatal jaundice due to glucose-6-phosphate dehydrogenase deficiency and was treated with phototherapy for two days (table 1).

Family history
Seven patients (28%) had consanguineous parents and four (16%) had a family history of febrile seizures. Three patients (12%) had parents or uncles with BIS. Three mothers had a history of one abortion and one with one neonatal death with unknown aetiology (table 1).

Gastroenteritis/rotavirus study
The frequency of diarrhoea ranged from two to four watery stools per day (table 1), and duration of diarrhoea from two to five days. Rotavirus was positive in the stools of 13 patients (52%). Stool specimens sent for bacterial culture showed no bacterial growth. Most of the cases occurred between April and September, peaking between June and July. Ten patients (40%) developed fever between 37.7°C and 38°C. In the remaining patients (60%) the GE was not associated with fever. No bloody stools were observed in any of the patients. Vomiting occurred in eight (32%) patients (table 1).

Investigations
Serum electrolytes, blood urea nitrogen, serum creatinine, liver function tests, urine and stool analysis, CSF study (if performed), and brain imaging were normal for all patients. All interictal EEGs were normal. Patient 5, a male with positive consanguinity, developed a cluster of three apparent GTCS after one day of mild diarrhoea, not associated with fever or vomiting (table 1). His ictal EEG showed right-side spike-wave complexes with no secondary generalisation (figure 2). None of the neuroimaging performed showed abnormalities.

Discussion
Fukuyama (1963) was the first author to introduce the concept of benign seizures occurring during infancy with a favourable outcome. In the last two decades, the existence of benign partial epilepsies during infancy with a good outcome has been recognized in many countries with different ethnic groups (Echenne et al., 1994; Caraballo et al., 2003; Callenbach et al., 2002; Saadeldin et al., 2010). The existence of benign infantile seizures (familial and non-familial types) in the Saudi paediatric population was confirmed in a previous
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Consanguinity</th>
<th>Age-presentation (months)</th>
<th>Personal/Family History</th>
<th>Age-current (months)</th>
<th>Interval (days) between GE and onset of seizures</th>
<th>Type of seizures</th>
<th>Number of diarrheal stools/vomiting per 5 days</th>
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<th>Rotavirus stools</th>
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Table 1. (Continued)

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<th>Age-current (months)</th>
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<th>Type of seizures</th>
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<th>EEG</th>
<th>Rotavirus stools</th>
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</table>

F: female; M: male; N: normal; GE: gastroenteritis; BIS: benign infantile seizures; FS: febrile seizures; C/S: caesarian section; G6PD def.: glucose 6 phosphate dehydrogenase deficiency; ND: neonatal death; EEG: electroencephalography; CT: computerized tomography; MRI: magnetic resonance imaging.
study, in which two patients were found to have BISwG (Saadeldin et al., 2010). The authors demonstrated that benign infantile seizures with favourable outcome are not uncommon in Saudi Arabia and are present in about 5% of the total patients with epileptic seizures during childhood (two months to 13 years) and about 12% of epilepsies during infancy (2-24 months) (Saadeldin et al., 2010). In 1982, Morooka was the first to report a clinical condition with an excellent outcome in which mild GE was associated with benign seizures during infancy. From various reports and series in the last three decades, it is clear that this entity, which is now referred to as BISwG, is common in Japan and Asia. Later, patients from other countries were reported with similar electroclinical features and outcome (Contino et al., 1994; Lynch et al., 2001; Caraballo et al., 2009; Narchi, 2004; Gómez-Lado et al., 2005). Currently, BISwG is considered by many as a benign situation-related seizure (Morooka, 1982; Uemura et al., 2002). To the best of the author’s knowledge, no reports of BISwG have been published in Saudi Arabia or other Arab countries. The present study demonstrates electroclinical features of BISwG similar to those of other studies (Kawano et al., 2007; Abe et al., 2000; Maruyama et al., 2007).

The age at seizure onset associated with GE in this series was 4-22 months. Some authors reported a higher age at onset of up to 60 months (Uemura et al., 2002; Gómez-Lado et al., 2005). Forty-four percent of the patients developed focal seizures, of which 27.2% developed focal and subsequent generalised seizures, 36% developed GTCS and in 20%, the seizures were not associated with a motor component. The recognition of focality in patients with BISwG is sometimes difficult for parents and even doctors (Caraballo et al., 2003). Focal features were described as hemiconvulsions, lateral gaze, or lateral posturing (Caraballo et al., 2003; Morooka, 1982; Uemura et al., 2002). For BISwG, many investigators have described the seizures to be generalised, based only on clinical features (Caraballo et al., 2003; Morooka, 1982; Uemura et al., 2002).

Nordli et al. (1997) analyzed 39 seizures in 20 infants recorded with simultaneous closed-circuit television and EEG. These recordings were independently, blindly reviewed by two epileptologists who concluded that clinical manifestations of seizures during infancy did not reliably indicate the laterality of a seizure or even whether a seizure was focal or generalised. Five patients in our study developed seizures in the form of staring and unresponsiveness with no apparent motor activity, which could not be confidently classified as either focal or generalised. Home video clips recorded for two patients were examined by a paediatric neurologist (IYS), who ascertained that these episodes were true seizures (see video sequence). Patient 5 developed generalised seizures, but his ictal EEG showed focal epileptiform discharges in the right parieto-occipital area with extension to the central area with no secondary generalisation (figure 2). This demonstrated that clinical manifestations of infantile seizures are variable and the distinction between partial and generalised seizures in infants can only be confidently made routinely by analyzing ictal EEG recordings preferably with the use of video-EEG monitoring (Nordli et al., 1997). Reports of ictal EEGs are rare in BISwG and all are reported as partial seizures with or without secondary generalisation (Uemura et al., 2002; Maruyama et al., 2007; Tsurui et al., 1989). The site of seizure origin varies among patients with BISwG and many have reported the seizure origin in frontal, temporo-parietal, centro-parietal and occipital areas and occurring mostly with secondary generalisation (Nordli et al., 1997; Imai et al., 1999), unlike that of the present patient. The site of seizure origin could not be confirmed in two cases of BISwG reported by Tsurui et al. (1989).

In the present study, 52% of patients had clusters of seizures and 48% had isolated seizures. Similar results have been reported (Komori et al., 1995; Caraballo et al., 2009; Maruyama et al., 2007). Uemura et al. (2002) reported a greater number of seizure clusters with two or more seizures occurring in 75% of patients. Others have reported multiple seizures to occur in 40-80% of patients with BISwG (Morooka, 1982; Komori et al., 1995). In the present study, the seizures occurred during the first five days of the onset of GE, and the duration of the seizures was brief and ranged from 25 seconds to two minutes; similar to previously reported cases (Uemura et al., 2002; Kawano et al., 2007; Abe et al., 2000). The diagnosis of BIS, in general, including BISwG, is determined by exclusion of symptomatic seizures. In this study, No patients showed any evidence of electrolyte or metabolic impairment which could be responsible for the seizures. Neuroimaging did not show any abnormalities.

BISwG should be differentiated from febrile seizures (FS) (table 2). As the name implies, FS are precipitated by fever which is usually more than 38 °C, unlike BISwG where the fever is absent or less than 38 °C (Verrotti et al., 2009). By definition, the age at seizure onset in FS is between six months and five years (peak at 18-22 months) (AAP, 2008) while the agreed age at onset in patients with BISwG is 4-30 months (Morooka, 1982; Uemura et al., 2002; Narchi, 2004). Other researchers limited the age at onset to less than two years (Abe et al., 2000). In patients with BISwG, clusters of seizures are common (Uemura et al., 2002; Komori et al., 1995; Caraballo et al., 2009; Narchi, 2004), unlike patients with simple FS. In the present series, although there is...
Table 2. Clinical characteristics and comparison between benign infantile seizures with mild gastroenteritis, febrile seizures, and nonfebrile illness seizures (Morooka, 1982; Uemura et al., 2002; Kawano et al., 2007; Verrotti et al., 2009; Zerr et al., 2005; Lee and Ong, 2004).

<table>
<thead>
<tr>
<th></th>
<th>Benign infantile seizures with mild gastroenteritis</th>
<th>Febrile seizures (simple)</th>
<th>Nonfebrile illness seizures (Afebrile seizures associated with minor infections)</th>
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<td>6-60 months</td>
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<td>Fever</td>
<td>&lt;38°C or absent</td>
<td>Usually &gt;38°C</td>
<td>Afebrile</td>
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<td>Isolated</td>
<td>Isolated</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Present (by definition)</td>
<td>Can be absent</td>
<td>Present (may be associated with rhinorrhea and cough)</td>
</tr>
<tr>
<td>Family history of febrile seizures</td>
<td>Rare</td>
<td>Common, familial with genetic predisposition</td>
<td>Rare</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>Infrequent</td>
<td>Common</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Excellent (later epilepsy not documented)</td>
<td>Very good (twofold excess of later epilepsy)</td>
<td>Very good</td>
</tr>
</tbody>
</table>

high incidence of consanguinity, genetic factors do not apparently play a major role in BISwG. Febrile seizures are often familial with a genetic predisposition (Hirose et al., 2003). Although the prognosis is excellent for both conditions, the recurrence rate appears to be low in patients with BISwG as shown in this series; a longer follow-up period may be required to confirm this. The differences between BISwG and FS suggest they are two separate conditions, but share some similarities (Uemura et al., 2002). It seems that there are seasonal differences in the prevalence of cases; while 80% of cases occurred during December to March in some studies, reflecting a winter prevalence of GE (Narchi, 2004), in this series the majority of cases occurred between April and September, peaking between June and July.

Another clinical entity with similarities to BISwG was considered by Lee and Ong (2004) to be a distinct type of situation-related seizure, which they referred to as “afebrile seizures associated with minor infections”. Later, Zerr et al. (2005) reported 36 children with first-time afebrile seizures occurring in the context of mild illness, characterized mainly by diarrhoea, vomiting, and rhinorrhea, which they referred to as “non-febrile illness seizures.” The authors compared the electroclinical features of these children with those of children with FS and unprovoked seizures (Zerr et al., 2005). Their data demonstrated an association between diarrhoeal illness and “non-febrile illness seizures”, and the condition appeared to have occurred as often as unprovoked seizures sharing characteristics with both FS and unprovoked seizures (table 2). The author’s opinion is that this entity could be a form of BISwG, and further viral analyses of stool specimens are warranted to establish the causal relationship.

Many studies have stressed that the presence of multiple seizures in clusters in patients with BISwG are rather refractory to antiepileptic drugs (Uemura et al., 2002; Kawano et al., 2007; Okumura et al., 2004). The clusters in the present series were brief and ceased spontaneously, and two patients only developed four seizures (16%).

The mechanism that causes seizures associated with mild GE is not fully understood. Viruses or viral fragments invading the central nervous system is one of the suggested mechanisms (Contino et al., 1994; Abe et al., 2000). Lynch et al. (2001) detected rotavirus
RNA in the CSF of two patients who developed encephalopathy. Brain dysfunction, caused indirectly by viruses, may be the effect of defects in neurotransmission through calcium channel abnormalities (Tian et al., 1996). High levels of nitric oxide (NO) in the serum may produce deleterious toxic effects to the brain (Kawashima et al., 2004). The authors found high levels of NO in these patients due to increased production of NO which may play a role in the pathogenesis of rotavirus-associated seizures (Kawashima et al., 2004). Moderate to severe GE causing significant dehydration and/or electrolyte imbalance and haemolytic uraemic syndrome may cause afebrile seizures. Although rotavirus disease is the single most important cause of GE in children in Saudi Arabia and throughout the world (Mohammed et al., 1994; El Assouli et al., 1992; Abe et al., 2000), seizures have been observed more commonly in children with GE caused by norovirus than by rotavirus infection (Chen et al., 2009). Kawano et al. (2007) studied 39 patients with BISwG and found that 30 patients were positive for rotavirus, nine patients were positive for norovirus, two patients were positive for sapovirus, two patients were positive for adenovirus, and one patient was positive for coxsackievirus A4. In this study, rotavirus antigen was positive in stools in 52% of the patients. The incidence of BISwG seems to be high in many Asian countries like Japan (Kawano et al., 2007; Abe et al., 2000) and Hong Kong (Wong, 2001), whereas it is uncommon in Europe and the United States (Contino et al., 1994). Seizures due to bacterial enteritis causing an encephalopathy-like picture may be specifically due to shigella (Ashkenazi, 2004), campylobacter (Solomon et al., 1982), and non-typhoidal salmonellosis (Arii et al., 2001).

The limitations of this study are the relatively small sample size, relatively short study period and the fact that the study was conducted in a tertiary referral hospital. The major strength of this study is the convincing confirmation that BISwG is not uncommon in Saudi Arabia. The prevalence of BISwG may be more common at the level of primary health centres, and it is hoped that such case series will increase the awareness of clinicians regarding the existence of this syndrome and its benign nature in children. The author stresses the importance of recognition of this benign condition in order to avoid unnecessary laboratory and neuroimaging investigations, EEG recordings and antiepileptic treatment. □

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Legend for video sequence
Patient 16. Video clip recorded at home using a mobile telephone of a nine-month-old boy showing staring with deviation of eyes to one side and no motor component, of about 40 seconds.

References
Benign infantile seizures with mild gastroenteritis


