Rev Med Int Sindr Down. 2014;**18(1)**:3-8

INTERNATIONAL MEDICAL REVIEW ON DOWN'S SYNDROME

www.elsevier.es/sd

FUNDACIÓ CATALANA SÍNDROME DE DOWN
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REVIEW

Down's syndrome and epilepsy

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Received on January 24, 2014; accepted on February 22, 2014

KEY WORDS
Epilepsy;
Seizures;
Down syndrome;
Infantile spasms;
Late-onset myoclonic epilepsy

Abstract
Down's syndrome (DS) is the most common genetic cause of mental retardation, affecting approximately one in 660 births. DS is associated with many neurological complications, including early-onset dementia that resembles Alzheimer's disease, Moyamoya disease, strokes, spinal ligamentous laxity, and epilepsy. The prevalence of epilepsy in individuals with DS is higher than in the general population, with rates ranging from 1% to 13%, with a mean of 5.5%. The increased seizure susceptibility in DS has been attributed to inherent structural and molecular anomalies of the brain and to secondary complications. Among other facts, patients with DS have less inhibitory γ-aminobutyric acid-containing granule cells and an increased level of glutamate, which favours a hyper-excitable state. West syndrome, with infantile spasms, is the most common epilepsy syndrome in children with DS. There are many electroencephalographic (EEG) anomalies associated with DS, but no specific pattern has been established. The primary drug choices for infantile spasms are adrenocorticotropic hormone, valproate and vigabatrine, but no significant difference has been demonstrated with different treatment options. Studies have shown that children with DS have better seizure control compared to other children with symptomatic infantile spasms. Other seizure types have been described in adult patients with DS including, focal crisis, reflex seizures, and late-onset myoclonic epilepsy associated with dementia. This article provides an overview of epilepsy in DS.

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PALABRAS CLAVE
Epilepsia;
Convulsiones;
Síndrome de Down;
Espasmos infantiles;
Epilepsia mioclónica de inicio tardío

Síndrome de Down y epilepsia

Resumen
El síndrome de Down (SD) es la primera causa genética de retraso mental: afecta aproximadamente a uno de cada 660 nacimientos. Se asocia con numerosas complicaciones neurológicas, como la demencia de inicio precoz (similar a la enfermedad de Alzheimer), la enfermedad de moyamoya, la laxitud de ligamentos espinales y la epilepsia. La prevalencia de epilepsia en individuos con SD es mayor que en la población en general, con tasas que varían entre el 1% y el 13% y una media del 5,5%. La mayor propensión de estos pacientes a desarrollar epilepsia está relacionada con anomalías estructurales y moleculares del cerebro y con complicaciones secundarias. También se sabe que poseen menos células que contienen gránulos de ácido γ-aminobutírico y una concentración mayor de glutamato que favorece un estado hiperexcitatorio.
El síndrome de West, con espasmos infantiles (EI), es el síndrome epiléptico más común en los niños con SD. Hay muchas anomalías en el electroencefalograma (EEG) asociadas con el SD, pero sin que se haya establecido ningún patrón específico. El esquema terapéutico de elección para los EI suele incluir hormona adrenocorticotropa, valproato y vigabatrina, pero no se ha demostrado que exista una diferencia significativa entre los distintos esquemas terapéuticos. Diversos estudios ponen de manifiesto que la población infantil con SD tiene un mejor control de la epilepsia cuando se compara con la de niños con EI asociados a otras causas. En adultos con SD se han descrito convulsiones focales, crisis reflejas y epilepsia mioclónica de inicio tardío asociada con demencia. En este artículo se presenta una revisión de la epilepsia en el SD.

Introduction

Down's syndrome (DS) is the most frequent genetic cause of mental retardation, affecting approximately one in 660 births[1,2]. It is associated with many neurological complications including, early-onset dementia, that resembles Alzheimer's disease, Moyamoya disease, infarctions, spinal ligamentous laxity, and epilepsy[3]. Gaete et al, found a prevalence of 38.7% of neurological problems in 253 children with DS, with oculomotor disorders and epilepsy being the most frequent[2,3]. Despite the fact that epilepsy was not included in the original description by John Langdon Down, it has been shown that its prevalence in DS is higher than that of the general population, but is lower than that of patients with mental retardation by other causes[4,5]. This article presents a review of the literature, including the epidemiology, pathophysiology, and clinical and therapeutic aspects of epilepsy in DS.

Epidemiology

Advances in medical care in DS from 1940 until the present has led to an increase in life expectancy, with a mean of 57.8 years for women and 61.1 years for men, which has made it necessary conduct further studies into some diseases, such as epilepsy, that can appear in adult life[6]. The onset of epilepsy in DS depends on age, and follows a triphasic distribution, with a first peak in infancy, another in early adulthood, and the last in patients over 50-55 years[1,7]. It is estimated that the epilepsy appears in 40% of cases in the first year of life, and in another 40% in the third decade[3]. The reported rates of epilepsy in Down's syndrome vary between 1% and 13%, with a mean of 5.5%. It is known that the prevalence of epilepsy increases with age, reaching 46% in individuals over 50 years old[8,9,10]. Several studies have found that the incidence varies depending on gender, boys who had a seizure had an age of onset earlier than girls, regardless of the type of seizures, and this could be due to the predominance of infantile spasms (IS) in boys, in whom the age of onset was less than one year[5,11].

Pathophysiology

The mechanisms that underlie greater susceptibility to develop epilepsy in individuals with DS are not fully known, but it is believed to be due to structural and molecular anomalies of the brain, as well as to secondary complications[3,5].

Among the structural anomalies of the brain in DS, are the decrease in neuronal density, and in particular, the number of inhibitory neurones, abnormal lamination of the cortex, and the persistence of the foetal morphology of the dendrites[9,11,12]. The volume of the hippocampus and the cerebellum is lower in boys with DS, and magnetic resonance studies have shown that the corpus callosum in this population has distinctive forms consistent with the characteristic brachycephaly of DS[13].

It is known that boys with DS have altered permeability to potassium at neuronal level, which leads to a decreased threshold in the generation of action potentials. A shorter hyperpolarisation period after the action potential, as well as a longer duration of the potential has also been described in this population[5,9,12]. It has also been found that there is a lower number of cells that contain γ-aminobutyric acid granules, as well as an increased level of glutamate that favours a hyper-excited state and the generation of seizures[3]. Furthermore, the concentrations of carbonic

anhydrase II, which potentially increases susceptibility to seizures, are elevated[14].

In DS there is an over-expression of the enzymes coded in the extra chromosome 21, and it is already known that several are actively transcribed. The superoxide dismutase-1 gene is in chromosome 21 and is overexpressed in approximately 50%, with the levels of superoxide decreasing and the hydrogen peroxide levels increasing[9]. The reduction in superoxide levels can alter the levels of peroxynitrite, nitric oxide and nitric oxide synthase, or the enzymes involved in aromatic hydroxylation, modifying neurotransmitter synthesis[5]. These structural, ion, and enzyme alterations, triggered by the primary genetic defect help to understand the reason why patients with DS are more susceptible to develop epilepsy.

In some cases, epilepsy may be considered as a complication of the cardiovascular changes observed in children with DS. Goldberg-Stern et al, found a relationship between cardiovascular anomalies and both partial and generalised seizures[5]. Within the cerebrovascular diseases associated with DS, it is worth mentioning the Moyamoya syndrome, which is a chronic occlusive vascular process that produces progressive stenosis of the internal carotid artery in its supraclinoid portion and main branches of the Willis polygon. This results in the generation of an anomalous collateral vascularisation network in the base of the brain to compensate for the lack of irrigation of the regions distal to the obstruction. The most frequent form of presentation in paediatric patients with Moyamoya syndrome is the ischaemic cerebrovascular accident (CVA), unlike in adults where haemorrhagic CVAs predominate. From a clinical point of view, unilateral neurological motor deficit is the most frequent presentation, and may be in an alternating hemiparesis or hemiplegia form. Besides the motor symptoms, patients may have sensory symptoms, involuntary movements, migraine, seizures, and cognitive impairment[15].

In adult patients with early-onset Alzheimer disease, the convulsions are frequent and are usually associated with genetic defects, including mutations in the gene of presenilin 1, which induces the overexpression of ß-amyloid. In animal models, it has been observed that the overexpression of amyloid precursor protein decreases the seizure threshold, and it is known that trisomy 21 causes an increase in the production of this protein that, in turn, causes an increase ß-amyloid, and subsequently seizures[10].

Clinical and electrophysiological findings

West syndrome is the most frequent epilepsy syndrome in children with DS[1,11]. IS is an age-dependent type of epilepsy that mainly presents in the first year of life. In a study by Osborne et al, on a sample of 207 children with infantile spasms, 2.4% had DS. Other studies have reported a frequency of IS in SD of between 3%-5%[8,16]. Several risks factors have been associated with IS in DS, such as prematurity, congenital heart disease, hypoxic-ischaemic encephalopathy, and encephalopathy associated with vaccination[1].

Comparing other populations with IS, a delay in the time of diagnosis of IS is observed in patients with DS. This could be due to the hypotonia that makes it difficult to see the flexion-extension pattern typical of IS, or to the presence of subtle seizures[2,8]. The most frequent EEG pattern of patients with IS and SD is the classic hypsarrhythmia, followed by modified hypsarrhythmia[11]. Children with DS and symptomatic IS do not usually have interictal paroxysmal activity, and the seizures are generally initiated by or combined with focal discharges[1]. In our experience the patients with IS and an abnormal EEG, but without hypsarrhythmia, have persistent seizures, and psychomotor development is severely affected[17] (fig. 1). Progression to Lennox Gastaut syndrome is less common than in other groups with West syndrome[3,8]. A series of patients with DS who developed delayed Lennox Gastaut syndrome has also been described, which was characterised by a greater frequency of reflex seizures and greater involvement at cognitive level (fig. 2).

All the main types of seizures have been described in DS patients[5]. Patients over 2 years-old usually have simple partial, complex partial, or tonic-clonic, seizures. Goldberg-Stern et al, evaluated 17 children with DS and found that 47% had suffered partial seizures, 32% IS, and 21% generalised tonic-clonic seizures. The tonic-clonic seizures appeared to have a more delayed age of onset [5]. Other seizures, such as focal, myoclonic and atonic, have been described in DS[1,3].

A high incidence of reflex seizures has been established in DS, most frequently in symptomatic and poorly controlled epilepsy[11]. Reflex seizures are usually triggered by sensory stimuli, and may be tonic, atonic, atypical absences, myoclonic, and generalised tonic-clonic[1].

The prevalence of epilepsy in DS increase with age, and now that life expectancy has increased, the approach to this comorbidity is becoming more important. Delayed onset epilepsy in the absence of dementia is uncommon. Adults over 45 years old with DS and seizures are more likely to develop signs of Alzheimer's disease, and around 84% of patients with DS and dementia develop seizures[18]. Once the seizures occur in the course of the dementia, the functional deterioration is rapid until the point that no cognitive assessments can be made. The dominant slowing down of occipital rhythm in the EEG appears to be associated with dementia in individuals with DS[10].

Late onset myoclonic epilepsy in DS is characterised by presenting after the fourth decade, with the presence of myoclonias, occasional generalised tonic-clonic seizures, and progressive dementia[7,10]. The cognitive impairment in this group can occur from 6 to 18 months before the onset of the seizures[19]. The pattern described in the EEG is of a slow activity with diffuse spike-wave and multispike-wave.

There are multiple anomalies in the EEG of individuals with DS, but no specific pattern has been identified[1]. Patients with DS have a voltage increase in all EEG bands, not necessarily associated with cognitive function. There is a decrease in the response to light stimulation at 12 Hz. Other studies have observed an increase in the voltage of theta and delta waves in children during sleep[9].

Treatment of epilepsy in Down syndrome

The pharmacological treatment of epilepsy must follow the same guidelines that are used in the general population.

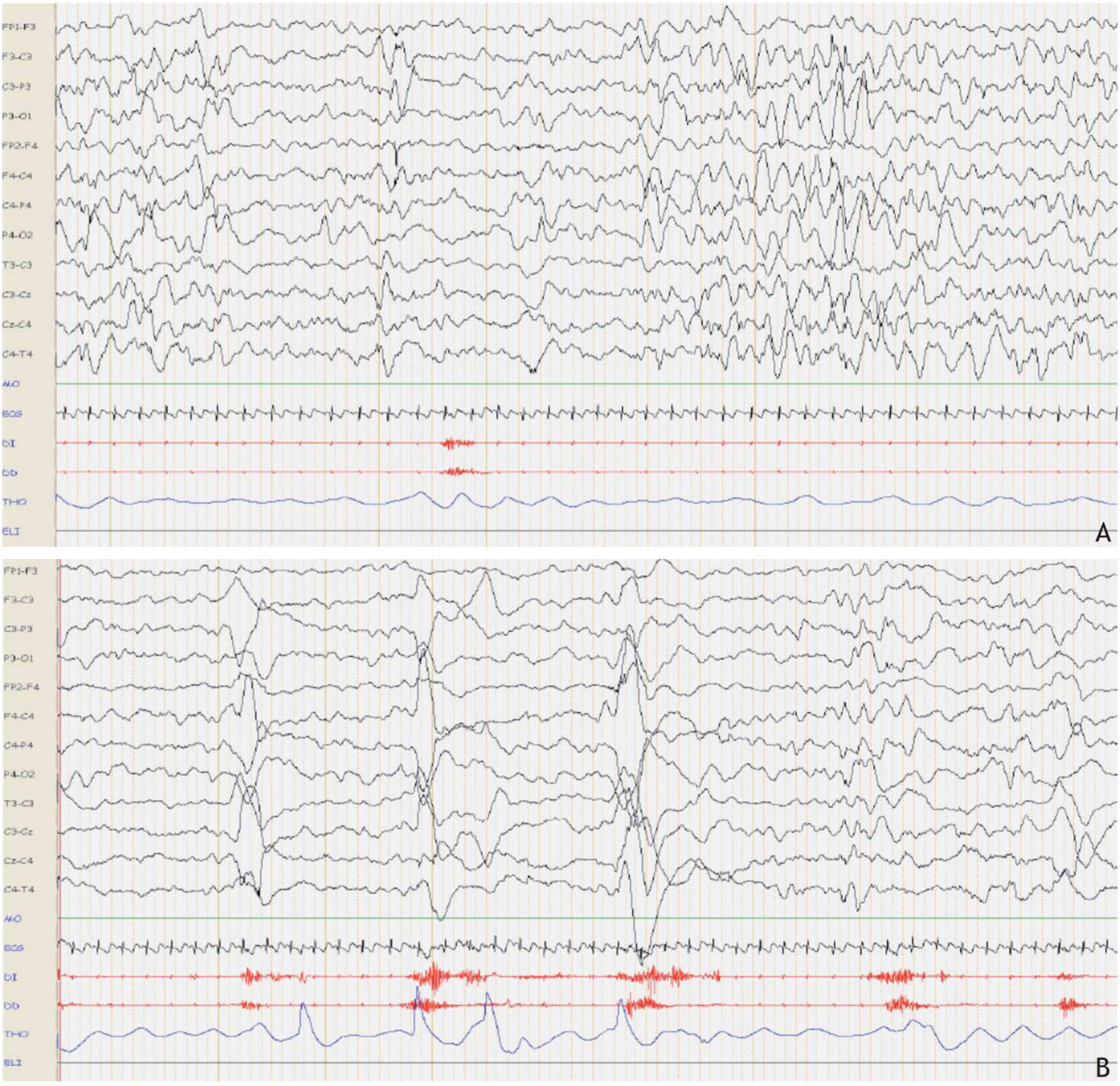

Figure 1 EEG of an 8 month-old child with Down syndrome with infantile spasms. A) During sleep, no physiological graph-elements are observed and there are very frequent multifocal paroxysms in the form of spikes-waves of elevated voltage. B) An electroclinical episode is observed that consists of the presence of an elevated voltage spike-wave complex accompanied by the extension of both upper limbs and a slight extension of the lower limbs. The muscular contraction of both deltoids is recorded by the surface electrodes.

The key is in an adequate classification of the seizures in order to choose the most appropriate drug. There is no uniformity in the anti-epileptic drug of choice, and this will depend on personal experience and on the protocols used in each hospital centre.

First choice drugs in IS in DS patients are adrenocorticotropic hormone, followed by vigabatrine and valproate, but no regimen has been shown to be clearly more effective, despite the greater tendency to use the first two[3,5,11,]. Fortunately, in several studies on patients with IS and DS, it has been confirmed that the responses to treatment and long-term control were better than expected, with response rates up to 90%, better than the cryptogenic (60-90%) and symptomatic IS (40-60%), or associated with other conditions[1,5,9,11]. It should be taken into account that there are relapses up to 2 years after the treatment with adrenocorticotropic hormone, therefore follow-up is very important even with a good initial response[8]. Other drugs that have been used to control children with DS and epilepsy are: pyridoxine, hydrocortisone, phenobarbital, phenytoin,

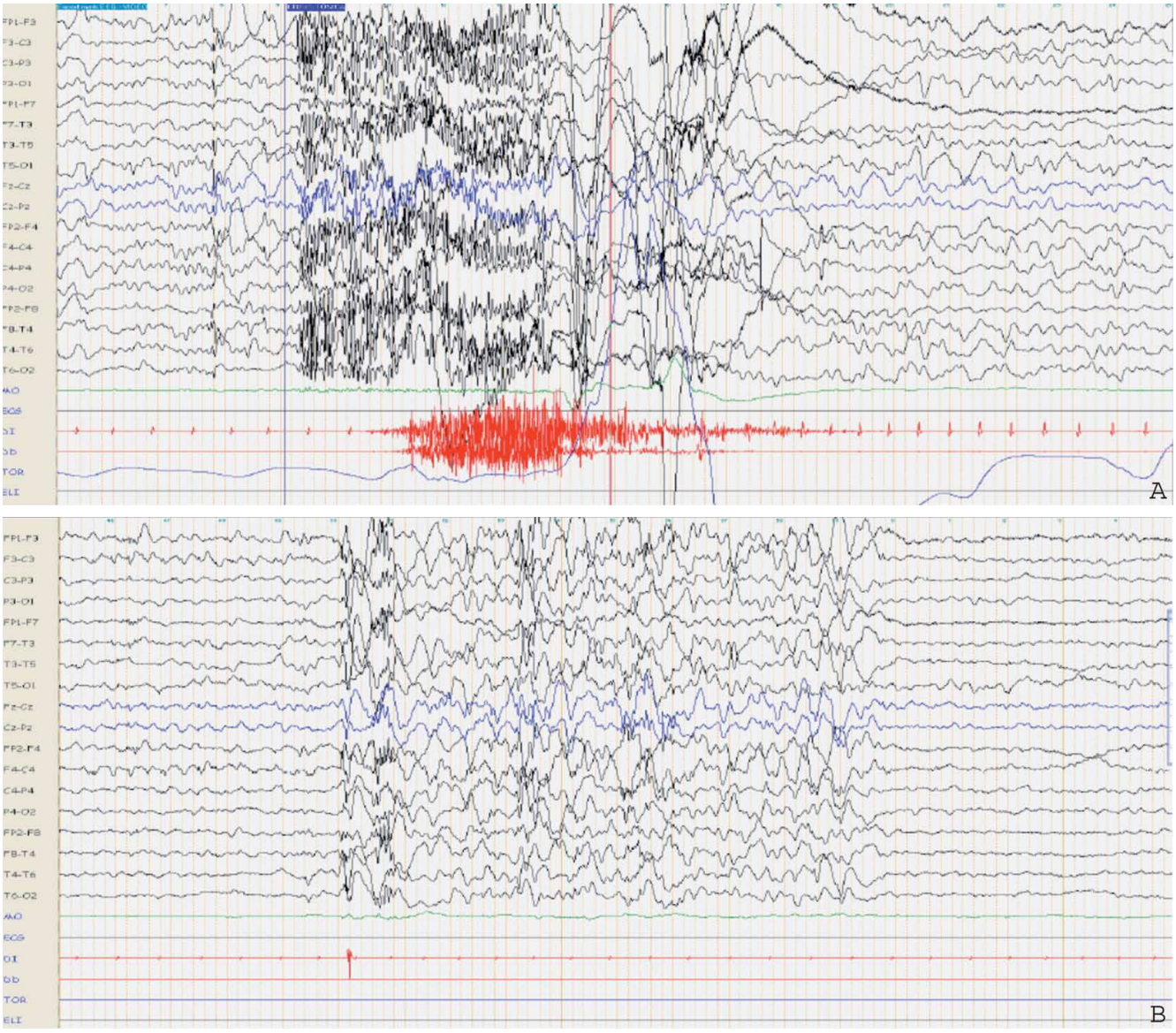

Figure 2 EEG of a 3 year-old boy with Down syndrome and West syndrome, which progressed to Lennox-Gastaut syndrome. A) A tonic seizure is observed: the ictal EEG shows medium-voltage biphasic waves followed by a rapid activity of low amplitude, replaced by a discharge of spikes and multi-spikes; the tonic muscular contraction is recorded in both deltoid muscles with surface electrodes. B) While awake, baseline activity is observed, made up of a combination of delta and theta waves and low amplitude beta rhythms. There are also focal paroxysms in the form of spikes and spike-wave complexes, independently located in the frontal and parietal-occipital regions of both hemispheres.

diazepam and primidone. It has not been possible to demonstrate any significant differences between the different regimens used to achieve clinical and EEG control[1]. In children with DS and IS, there appears to be a significant association between a delay in starting anti-epileptic treatment and the development coefficient. It is difficult to assess neurodevelopment in this population due to comorbidities common to the syndrome, and to the lack of a specific scale for DS. However, it seems that a delay in starting treatment of more than 2 months may predict the persistence of the seizures, and this negatively influences neurodevelopment and autistic behaviour[1,11].

In children with partial seizures, good control has been reported with carbamazepine and with valproate as single therapy, and a good response to valproate also as single therapy in generalised seizures. Higher rates of refractory epilepsy are reported in this group of patients. In a study performed by Verotti et al, about one third of the patients required combined therapy[11].

Adequate control with valproate, topiramate and levetiracetam has been achieved in DS adults with late onset myoclonic epilepsy[7,19]. Topiramate must be used with caution since it can cause greater cognitive impairment[7].

There is an increased risk of sudden death in individuals

with DS and poor controlled epilepsy, which has been attributed to factors such as: presence of generalised tonic-clonic seizures, early onset of the epilepsy, multiple therapy with antiepileptic drugs, presence of cardiac arrhythmias, water-electrolyte balance, and duration of the epilepsy[20]. This leads us to emphasise the need for an integral approach and management of these patients by a multidisciplinary team with special emphasis on control of the epilepsy.

Conclusions

Patients with DS are more susceptible to suffer from epilepsy, and this may have negative repercussions on their neurodevelopment. The findings of the last decade highlight the importance of the early detection and treatment of this complication, with the aim of optimising the development and quality of life of these patients. For this reason, it is very important that doctors are aware of the association between DS and epilepsy. A high index of clinical suspicion and an appropriate anamnesis are key for the early diagnosis. It is essential to take the necessary time to explain the characteristics of epilepsy, as well as the importance of its maximum control and management to the families, in a simple and clear manner.

Acknowledgments

We would like to express our gratitude to all the patients with DS and their families, to the members of the Epilepsy Unit of the Neurology Department of the Hospital Sant Joan de Déu, the members of the Down's Medical Centre, members of the Catalan Down's Syndrome Foundation, and to our families for their constant support and time.

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