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Down Syndrome and Epilepsy

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1. Introduction

Down syndrome (DS) is associated with many neurological complications including cognitive deficits, early-onset dementia -which resembles Alzheimer's disease- and seizures. Although seizures and epilepsy were not mentioned in the original description of DS (Down, 1866) the prevalence of seizures in individuals with DS is now known to be higher than in the general population, but lower than in patients with some other types of mental retardation (Corvett et al., 1975). Reported rates of epilepsy in DS range from 1 to 13% (see table 1) (Tatsumo et al., 1984). Individual series are difficult to compare because of differences in inclusion criteria and study populations. The increased seizure susceptibility in DS has been attributed to inherent structural and molecular anomalies of the brain or to associated medical complications, such as cardiovascular abnormalities and recurrent infections.

Medical interventions in DS have resulted in increased longevity, with estimated life expectancy of people with DS in developed countries increasing from an average of 12 years in the 1940s to an average of 57,8 years for women and 61,1 years for men (Bittles et al., 2007). Epilepsy onset in people with DS is age-specific; therefore, because certain complications will arise in childhood and others in adulthood, their occurrence is relevant to paediatric and adult neurologists. This chapter will provide a critical overview of epilepsy in DS.

Authors	No. of patients	Percentage (%)
Romano et al.	113	13.00
Pueschel et al.	405	8.10
Stafstrom et al.	737	6.40

Table 1. Reported incidence of seizures in patients with Down syndrome in the 1990s

2. Epidemiology

Patients with DS show a higher incidence of febrile and non febrile seizures than non-DS individuals. Seizures occur in a bimodal distribution in DS, with 40% of individuals first developing seizures before 1 year of age and another 40% having an onset in their thirties or

later (Pueschel et al., 1991). Boys tend to have an earlier age onset, regardless of seizure type, although this may reflect the general male predominance in the infantile spasm group aged less than 1 year at onset. The prevalence of epilepsy increases with age and reaches 46% in those over 50. In general, about 8% of patients with DS have seizure disorders: 47% of them develop partial seizures, 32% infantile spasms and 21% generalized tonic-clonic seizures.

3. Pathophysiology

The mechanisms underlying the increased seizure susceptibility in DS have not yet been completely elucidated. Seizures in infancy have been linked to inherent structural brain abnormalities, such as fewer inhibitory neurons, abnormal cortical lamination, persistent fetal dendritic morphology, and underdeveloped synaptic profiles (Kemper et al., 1988). Concentrations of carbonic anhydrase II, which potentially increases seizure susceptibility, are upregulated in the brains of young children with DS and in a mouse model of the disorder. (Palminello et al., 2008) (Tatsuno et al., 1984).

Altered membrane potassium permeability, which may lead to a decreased voltage threshold for spike generation, smaller hyperpolarization following spikes, or increased action potential duration, has also been documented in patients with DS. Indeed, in the mouse model of trisomy 16, the experimental model of DS, a rapid spike rise and fall was recorded from the dorsal root ganglia neurons (Scott et al., 1981)

In DS there is an overexpression of the 21st chromosome. Many enzymes that are encoded on the extra 21st chromosome are known to be actively transcribed, which results in overexpression of the enzymes, overconsumption of enzymatic substrates and overproduction of metabolic end-products. For example, the superoxide dismutase-1 gene on the 21st chromosome is approximately 50% overexpressed, which decreases levels of superoxide (the enzyme's substrate) and increases levels of hydrogen peroxide (the enzyme's metabolite, end product or output). These primary consequences of genetic overexpression may then produce secondary metabolic adaptations as homeostatic systems attempt to compensate. Thus, decreased levels of superoxide might alter levels of nitric oxide, peroxynitrate, and nitric oxide synthetase, or they may impair aromatic hydroxylation enzymes and thereby impair neurotransmitter synthesis. For another example, increased levels of hydrogen peroxide might induce glutathione peroxidase production and thereby increase selenium requirements. Such genetically driven enzymatic and metabolic disturbances may help explain why individuals with DS appear to be more likely to develop various forms of epilepsy and intractable epilepsy (Smigielska-Kuzia et al. 2009).

Seizures can also be regarded as complications of congenital cardiovascular anomalies in children with DS (Marsh et al., 2009). Moyamoya's disease is a rare vascular complication which seems to occur with a higher frequency in children with DS than in those without it. Moyamoya's disease is characterised by a chronic occlusive cerebrovascular alteration of unknown pathogenesis in which there is progressive stenosis of the supraclinoid portions of the internal carotid arteries. Associated with this stenosis is the formation of convoluted arterial collaterals at the base of the brain. Although the presentation of Moyamoya's disease in adults is haemorrhagic, the presenting symptoms in children are typically ischaemic, with a fixed unilateral neurological deficit or alternating hemiplegia. Some children with Down's syndrome who have Moyamoya's disease also develop seizures or involuntary movements. (Nascimento et al. 2006).

Adult-onset seizures in the absence of dementia are rare in people with DS but might become more frequent in the future because of the extension of the lifespan of people with the disorder. Late-onset seizures in people with DS seem to be associated with a propensity to dementia resembling Alzheimer's disease. The cause of seizures in adults with DS who do not have dementia is not yet clear (Puri, 2001)

Once seizures occur in the course of dementia in patients with DS, functional decline is often rapid, to the point where floor effects preclude further cognitive testing. Seizures are common in people with early-onset Alzheimer's disease associated with genetic defects, including mutations that result in overexpression of amyloid-β, such as those involving presenilin 1 genes. Animals with overexpression of the APP gene have a lower threshold to induced seizures. High concentrations of amyloid-β caused by APP overexpression result in epileptiform activity in vivo, even in the absence of neurodegeneration, suggesting that these high concentrations are a direct cause of epilepsy. (T Llot 2010).

4. Clinical and electrophysiological features

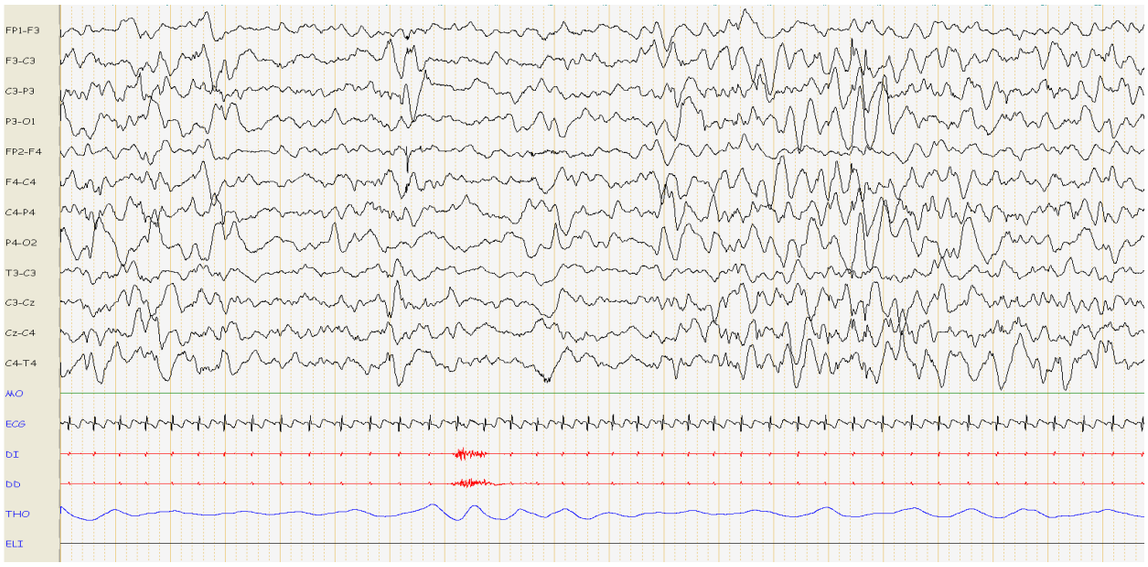
Epilepsy in DS showed a bimodal distribution; in the younger age group, infantile spasms and tonic-clonic seizures with myoclonus are the main finding, whereas older patients often have partial simplex or partial complex seizures as well as tonic-clonic seizures (Pueschel et al., 1991).

4.1 Seizures in infancy and childhood

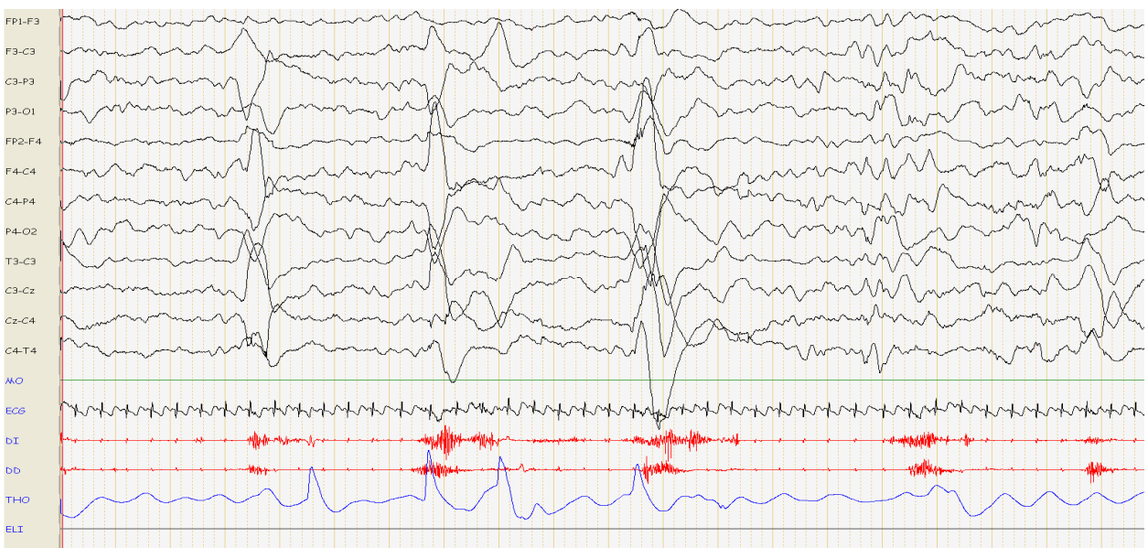
It is currently known that there is a higher incidence of seizures, particularly infantile spasms, in DS compared to the general population. Few children with DS have their first epileptic attacks after the age of 3. These patients often have partial simplex or partial complex seizures as well as tonic-clonic seizures.

Infantile spasms are an age-dependent epilepsy that most frequently appears in the first year of life, with ictal episodes consisting of spasms that usually occur in clusters (Dulac et al., 1994). There is a characteristic chaotic and high-voltage interictal electroencephalography (EEG) pattern, which, when typical, is called hypsarrhythmia. *West's syndrome* is the term employed when such spasms are concomitant with delayed psychomotor development and EEG hypsarrhythmia. It has been reported that 6.4% of 737 patients with DS had epilepsy, and 12.8% of epileptic patients with DS had West syndrome. In addition, it has been reported that 8.1% of 405 patients with DS had epilepsy in childhood, and 18% of the epileptic patients were diagnosed as having infantile spasms.

Infantile spasms, which often indicate poor prognosis in the general population, do not seem to be associated with difficulties in long-term seizure control in children with DS. However, in children with DS who have infantile spasms, there seems to be a substantial association between treatment and developmental quotient as well as progression to autistic features. There are no long-term studies of the intellectual outcome of children with DS in whom infantile spasms were successfully controlled. In our experience, patients with Down syndrome with infantile spasms and abnormal but non-hypsarrhythmic EEG may have poor disease progression (figure 1 a and b & Figure 2 a and b), with persistence of seizures and severely impaired psychomotor development (Nascimento & Ortez 2009).

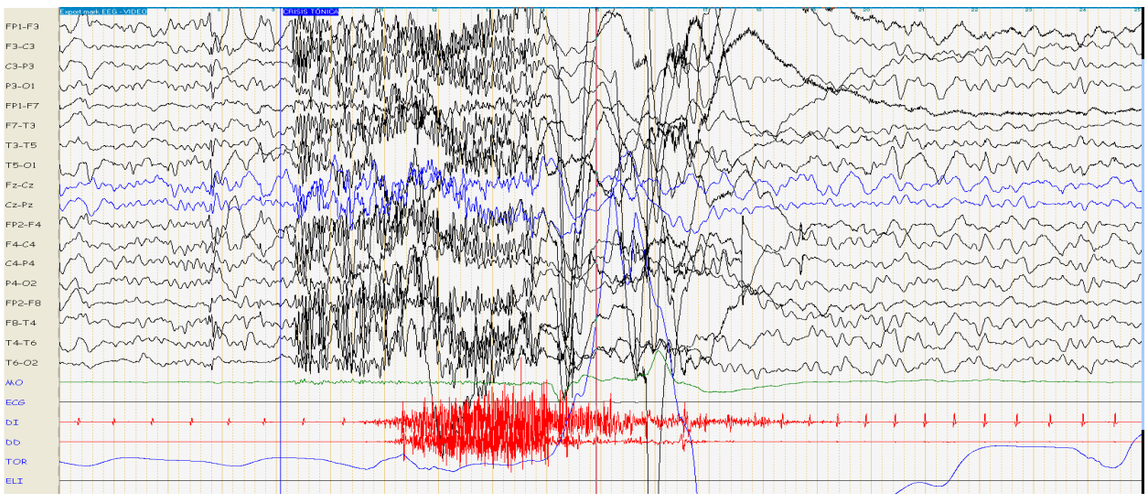


a)



b)

Fig. 1. EEG of an 8m21d boy with DS. a) In a sleep stage, no physiological graphoelements were observed and there were very frequent multifocal paroxysms in the form of high-voltage spike-wave complexes; paroxistic alterations persisted during the waking stage. b) There was an electroclinical episode consisting of the emergence of a high-voltage spike-wave complex clinically accompanied by extension and abduction of the upper limbs and a slight extension of the lower limbs. Note the contraction recorded over both deltoid muscles.



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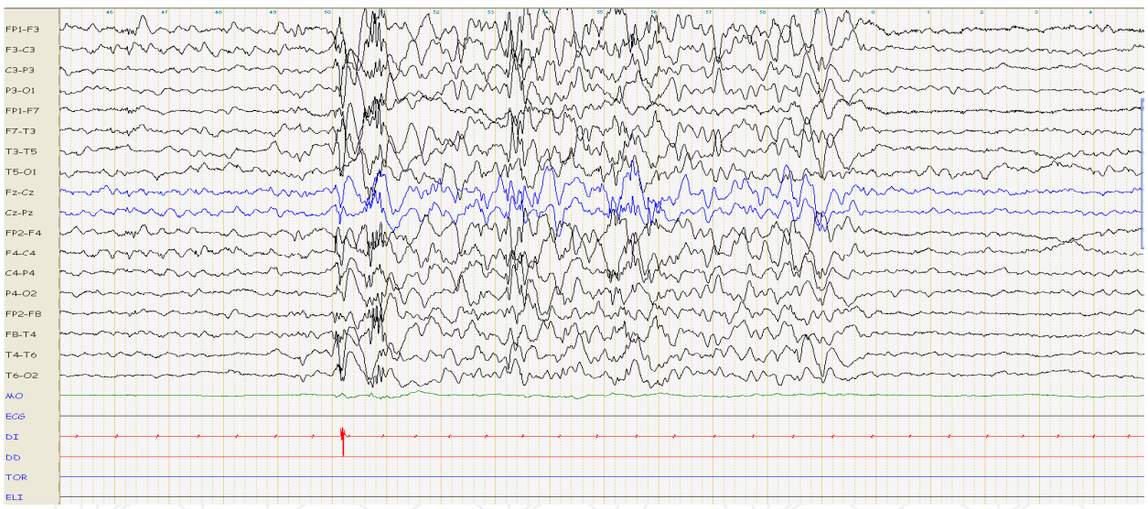

b)

Fig. 2. EEG of a 3-year-old girl with DS initially affected by West's syndrome who then evolved to Lennox-Gastaut syndrome. a) Tonic seizure: Ictal electroencephalography (EEG) shows a diphasic, mid-voltage slow wave, followed by recruiting low-voltage fast activity, replaced by spike and polyspike and wave discharges; tonic contraction was recorded over both deltoid muscles. b) Waking stage: brain activity constituted by an association of delta and theta waves and low-voltage beta rhythms, with a diffuse distribution. Frequent focal paroxysms were observed in the form of spikes and complex spike-waves of irregular medium and high amplitude, located independently in the frontal and parieto-occipital regions of both hemispheres.

There is a chance that DS in association with West's syndrome may evolve to Lennox-Gastaut syndrome (LGS). LGS has classically been defined by the triad of drug-resistant epilepsy with multiple seizure types, typically diurnal atonic as well as atypical absences, and mainly nocturnal tonic seizures; electroencephalography abnormalities, principally diffuse slow spike-wave or polyspike-wave discharges during wakefulness and bursts of diffuse fast rhythms at 10–20 Hz during sleep; mental deterioration of variable severity as well as behavioural disturbances may also occur (Gastaut et al., 1966; Dulac & N'Guyen, 1993). A series of DS patients with late onset LGS has been described, having a higher frequency of reflex seizures and more cognitive impairment (Figure 3). (Ferlazzo et al., 2009)

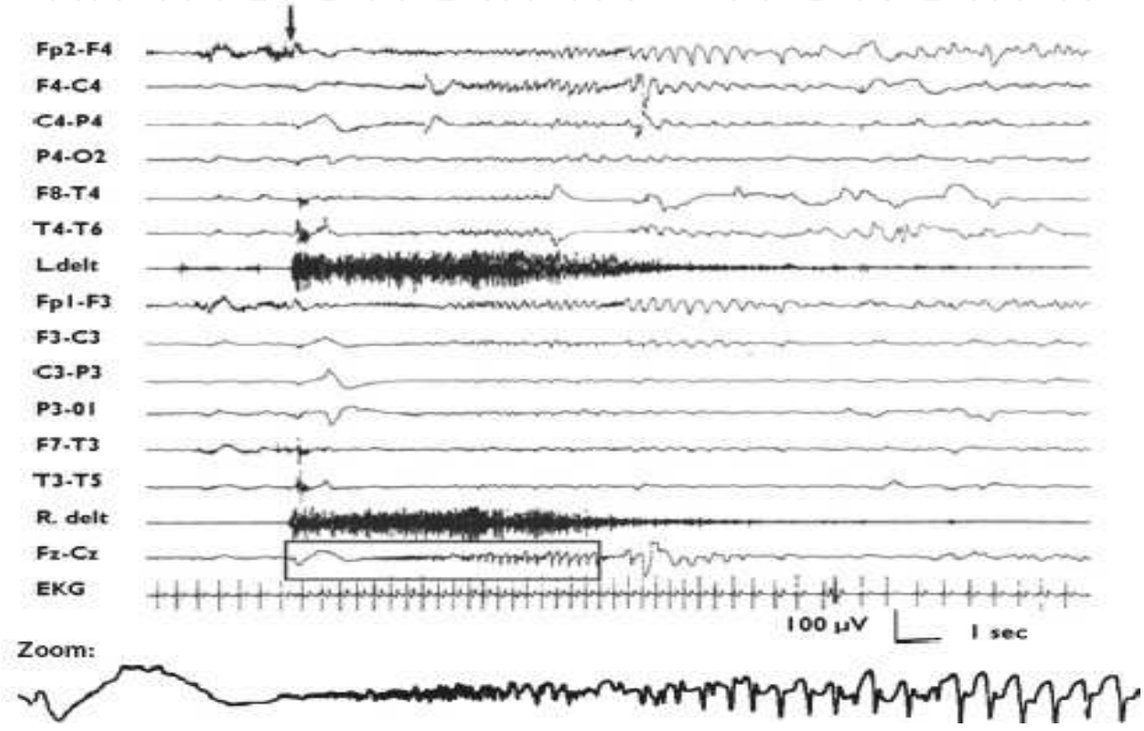

Fig. 3. 7-year-old boy. Tonic seizure triggered by a sudden noise (black arrow). Note the marked tonic contraction recorded over both deltoid muscles. Ictal electroencephalography (EEG) shows a diphasic, mid-voltage slow wave, followed by recruiting low-voltage fast activity, replaced by spike and polyspike and wave discharges, predominant over anterior leads, lasting for about 10 s. Electrocardiography shows an increased heart rate during seizure. Zoom: detail of the ictal discharge recorded over the vertex derivation, where muscular artifacts are less evident. (Ferlazzo et al. 2009)

Why do some infants with DS develop infantile spasms, whereas others with the same disorder do not? The cause has never been fully understood. Naming DS as the ''cause'' of the infantile spasms may, therefore, be at best inaccurate and at worst totally misleading, suggesting that we understand why the disorder has arisen in that particular child when DS has merely predisposed the child to infantile spasms. Only a few infants with Down syndrome develop infantile spasms, yet Down syndrome is accepted (Eisermann et al., 2003) as a ''cause,'' and frequently such infants are not given a brain scan. As a result, other authors have proposed adopting a terminology that distinguishes the underlying etiology

from the cause. According to this scheme, we use the term *proven etiology* to refer to any identified underlying neurological disorder, and employ *cause* as a more specific term that may be a complex and less well-understood sequence or combination of events. Perhaps because of the many different diagnoses that can be made in these infants and the developmental outcomes associated with them, classification into diagnostic groups has been commonly attempted. (Osborne et al., 2010)

The most frequent nomenclature has classified cases as either symptomatic, cryptogenic, or idiopathic, but unfortunately there is no clear definition of these terms (Lux & Osborne, 2005). "Symptomatic" is often used to indicate that a prior disorder exists. "Cryptogenic" is often used to mean that there must be an etiology, but that one has not been found. A recent report of the International League Against Epilepsy (ILAE) Commission on Classification and Terminology also suggests that the terms idiopathic, symptomatic, and cryptogenic should be replaced (Berg et al., 2010). It has suggested broad etiologic categories: genetic, structural–metabolic, and unknown.

4.2 Seizure in adulthood

The prevalence of epilepsy in DS has increased with longevity, reaching 46% in those older than 50. Descriptions of late-onset epilepsy in the absence of dementia in DS patients (LOMEDS) are rare, but since life expectancy of DS patients has markedly increased, LOMEDS may be more frequent than currently acknowledged and should be considered in the differential diagnosis of adult-onset myoclonic epilepsies. The electroclinical features are myoclonic jerks on awakening and generalised tonic-clonic seizures, with generalised spike and wave on EEG, and progressive dementia (Moller et al., 2002).

Familial Alzheimer's dementia (FAD) and progressive myoclonic epilepsy (Unverricht–Lundborg type) are both linked to chromosome 21. In an interesting study of 68 DS adults, it was found that among those with a history of seizures, individuals aged over 45 years were significantly more likely to develop AD than those under 45, and up to 84% of demented individuals with DS developed seizures. It suggests that late-onset epilepsy in DS is associated with AD, while early-onset epilepsy is associated with an absence of dementia (Menéndez, 2005).

Seizures in adults with DS differ from those in adults with Alzheimer's disease who do not have DS: myoclonic seizures usually occur late in the course of Alzheimer's disease whereas partial or tonic–clonic seizures occur in adults with Down's syndrome and are often precursors to cognitive decline. Adults with DS aged over 45 years who have seizures are substantially more likely to develop signs of Alzheimer's disease (Puri et al; 2001). Once seizures occur in the course of dementia in patients with DS, functional decline is often rapid, to the point where floor effects preclude further cognitive testing. Seizures are common in people with early-onset Alzheimer's disease associated with genetic defects, including mutations that result in overexpression of amyloid-β, such as those involving presenilin 1 genes.

Animals with overexpression of the *APP* gene have a lower threshold to induced seizures. High concentrations of amyloid-β caused by *APP* overexpression result in epileptiform activity in vivo, even in the absence of neurodegeneration, suggesting these high concentrations directly as a cause of aberrant neuronal network synchronisation. Slowing of the dominant occipital rhythm seems to be associated with dementia in individuals with DS, and the frequency of dominant occipital activity decreases as cognition deteriorates.

4.3 Seizure in Alzheimer´s and DS

Despite the apparent clinical heterogeneity in aged individuals with DS, age-associated AD-like neuropathology is a consistent feature. This is due to the fact that trisomy 21 leads to a dose-dependent increase in the production of the APP and subsequently the production of the amyloidogenic fragments leading to early and predominant senile plaque formation.
Ten percent of patients with AD have seizures, and another 10% have myoclonus. The incidence of seizures is about 10 times higher than expected in a reference population. Both seizures and myoclonus, individually or together, are manifestations of AD and may be seen at any time in the course of the illness, but myoclonus is often a late manifestation. (Volicer et al., 1995)

4.4 Electroencephalography (EEG) features

Individuals with DS have increased absolute power in all the EEG bands, independent of cognition functions. In the power spectrum of the resting EEG, there is a cognition-related increase in power at theta- and alpha-slowing. Furthermore, in the stimulated EEG, there are several cognition-related abnormalities, such as decreased responses to 12-Hz stimulation and decreased integral of beta- and gamma-band responses, indicative of decreased responsiveness to photic stimulation. Other reports note an increase in power at theta and delta in children with DS during sleep. (S'migielska-Kuzia et al., 2009). There is a significant increase in theta, delta, and beta power and a decrease in alpha compared with non-DS with epilepsy. (Figure 3)

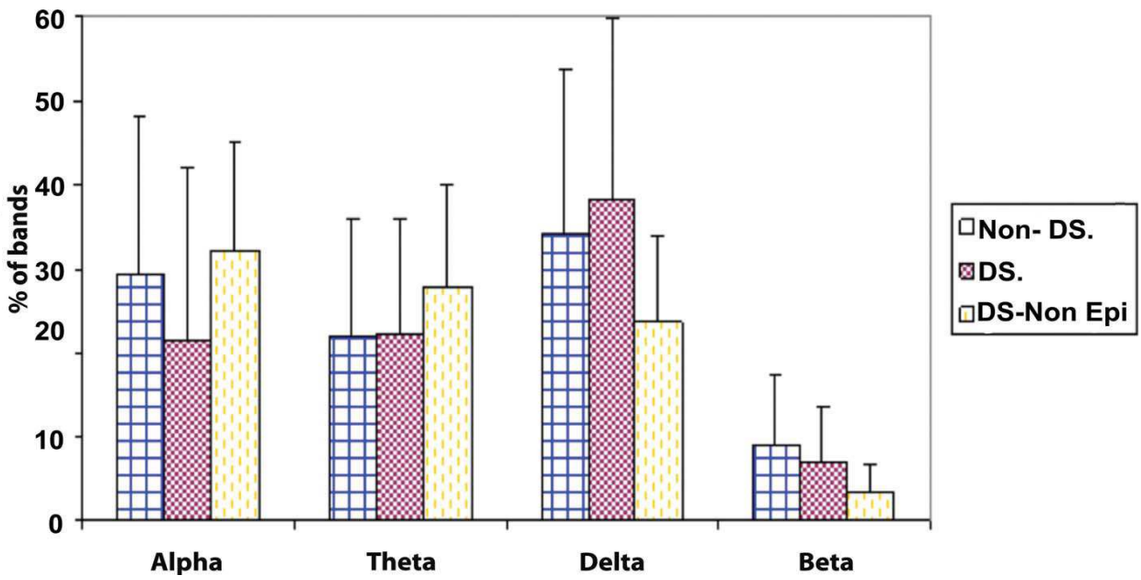

Fig. 3. Spectral power of alpha, theta, delta, and beta bands of DS, n = 12, DS Non-Epilepsy (Non-Epi) n=10 versus Non-DS (epileptic children) n = 28. Alpha Non-DS versus alpha DS P < .001; alpha Non-DS versus alpha DS Non-Epi P = .001; alpha DS versus alpha DS Non-Epi P < .001; theta Non-DS versus theta DS P = .767; theta Non-DS versus theta DS Non-Epi P < .001; theta DS versus theta DS Non-Epi P < .001; delta Non-DS versus delta DS P < .001; delta Non-DS versus delta DS Non-Epi P < .001; delta DS versus delta DS Non-Epi P < .001;beta Non-DS versus beta DS P < .001; beta Non-DS versus beta DS Non-Epi P < .001; beta DS versus beta DS Non-Epi P < .001. (S'migielska-Kuzia et al., 2009)

5. Treatment of epilepsy in DS

The pharmacological treatment of epilepsy in DS is no different from that of other patients diagnosed with epilepsy; the key is proper clinical and electrical classification to guide epilepsy treatment and thereby obtain good therapeutic results.

Although the cognitive profiles of newer antiepileptic drugs (AEDs) are in general better than those of older antiepileptic drugs, neurological adverse events do occur, including somnolence, distractibility, dizziness, and an altered pattern of sleep architecture. Individuals with DS have an unusually high number of side-effects from phenytoin (Tsiouris et al., 2002).

Over time, with the advent of advances in molecular biology, many AEDs have been uncovered, so they have come to be classified as first-, second- and third-generation drugs. (see table 2)

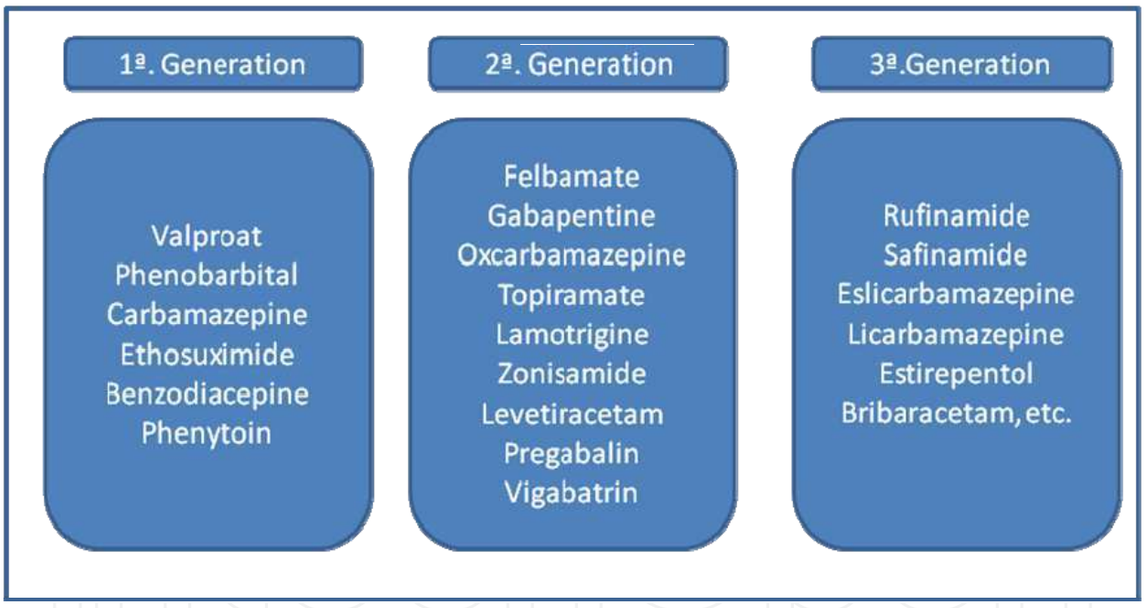

Table 2. Antipileptica drugs by generation

Figures 4 a & b and table 3 describe the different mechanisms of action demonstrated for antiepileptic drugs (AEDs).

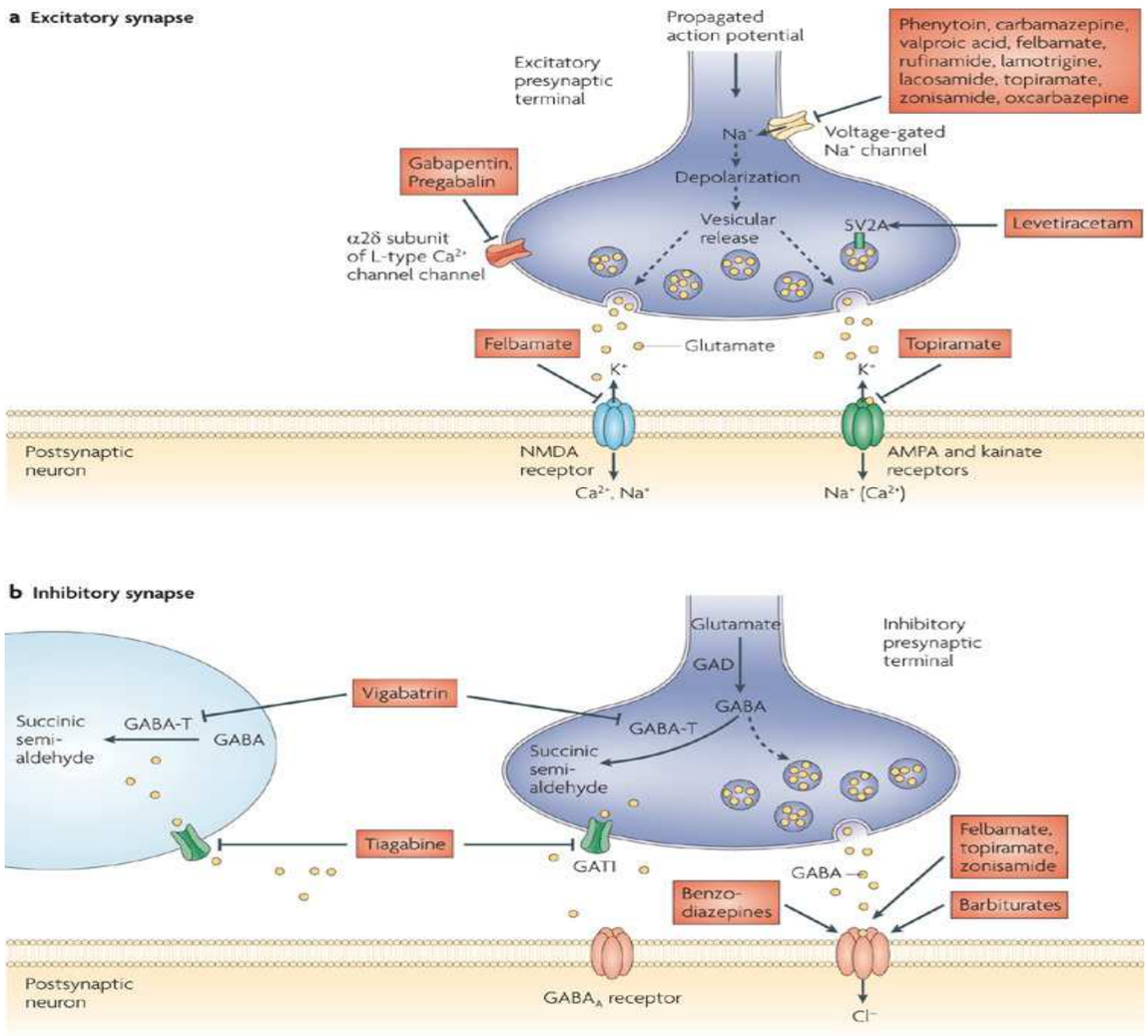

Fig. 4. a& b Proposed mechanisms of action of currently available AEDs at excitatory and inhibitory synapses.

a | Currently available antiepileptic drugs (AEDs) are thought to target several molecules at the excitatory synapse. These include voltage-gated Na^+ channels, synaptic vesicle glycoprotein 2A (SV2A), the α2δ subunit of the voltage-gated Ca^{2+} channel, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, and NMDA (*N*-methyl-D-aspartate) receptors. Many of the AEDs can modulate voltage-gated Na^+ channels. This would be expected to decrease depolarization-induced Ca^+ influx and vesicular release of neurotransmitters. In addition, lacosamide is thought to enhance slow inactivation of voltage-gated Na^+ channels. This effect is different from that of other listed AEDs, which are thought to enhance fast inactivation. Levetiracetam is the only available drug that binds to SV2A, which might have a role in neurotransmitter release. Gabapentin and pregabalin bind to the a2δ subunit of voltage-gated Ca^{2+} channels, which is thought to be associated with a decrease in neurotransmitter release. Excitatory neurotransmission at the postsynaptic membrane can be limited by topiramate (acting on AMPA and kainate receptors) and felbamate (acting on NMDA receptors).

b | AED targets at inhibitory synapses have also been proposed. These include the g-aminobutyric acid (GABA) transporter GAT1 (also known as SLC6A1), which is inhibited by tiagabine, leading to a decrease in GABA uptake into presynaptic terminals and surrounding glia; and GABA transaminase (GABA-T), which is irreversibly inhibited by vigabatrin. This decreases the metabolism of GABA in presynaptic terminals and glial cells. The benzodiazepines, barbiturates, topiramate and felbamate have been found to enhance inhibitory neurotransmission by allosterically modulating $GABA_A$ receptor-mediated Cl^- currents. However, the action of each of these drugs is different and is dependent on the subunit conformation of the $GABA_A$ receptor complex. GAD, glutamic acid decarboxylase. (Bailer & White 2010).

	Blockade of voltage-dependent sodium channels	Increase in brain or synaptic GABA levels	Selective potentiation of $GABA_A$-mediated responses	Direct facilitation or chloride-ion influx	Blockade of calcium channels	Other actions
First generation AEDs.						
Benzodiazepines	-	-	++	-	-	-
Carbamazepine	++	?	-	-	+	+
Ethosuximide	-	-	-	-	++	-
Phenobarbital	-	+	+	++	?	+
Phenytoin	++	-	-	-	?	+
Valproic acid	?	+	?	-	+	++
Second generation AEDs.						
Felbamate	++	+	+	-	+	+
Gabapentin	?	?	-	-	++	?
Lamotrigine	++	+	-	-	++	+
Levetiracetam	-	?	+	-	+	++
Oxcarbamacepine	++	?	-	-	+	+
Pregabalin	-	-	-	-	++	-
Tiagabaline	-	++	-	-	-	-
Topiramate	++	+	+	-	+	+
Vigabatrin	-	++	-	-	-	-
Zonisamide	++	?	-	-	++	+

++ primary action; + secundari action; -, no action described; ?, controversial evidence.

Table 3. Main Mechanism of action of AEDs.

Table 4 describes the different AEDs and the main indication for the type of epilepsy diagnosed. Table 5 describes the AEDs, dose in children and adults and side effects.

FIRST GENERATION AEDs	MAIN INDICATION
Benzodiazepines	Status epilpeticus. Partial an generalizated seizures
Carbamazepine	Partial seizures (with and whithout secondary generalization) and primarily generalized tonic-clonic seizures.
Ethosuximide	Absence seizures, continuous spike – waves during slow sleep.
Phenytoin	Partial seizures (with and whithout secondary generalization) and primarily generalized tonic-clonic seizures. Status epilepticus.
Valproic acid	Generalized and partial seizures. Status epilepticus.
SECOND GENERATION AEDs	MAIN INDICATION
Felbamate	Severe epilepsies, particulary Lennox-Gastaut syndrome, refractory to all other AEDs.
Gabapentin	Partial seizures (with and whithout secondary generalization)
Lamotrigine	Partial and generalized seizures (may aggravate severe myoclonic epilepsy of infancy)
Levetiracetam	Partial and probably generalized seizures.
Oxcarbamacepine	Partial seizures (with and whithout secondary generalization) and primarily generalized tonic-clonic seizures.
Pregabalin	Partial seizures (with and whithout secondary generalization).
Tiagabaline	Partial seizures (with and whithout secondary generalization).
Topiramate	Partial and generalized seizures (efficacy against absence seizures not proven)
Vigabatrin	Infantile spasms and West Sindrome. Partial seizure (with and whithout secondary generalization) refractory to all other AEDs.
Zonisamide	Partial and, probably, generalized seizures.

Table 4. AEDs and the main indication for the type of epilepsy diagnosed

AEDs	Childrens Dose mg/kg/d	Adults Dose mg/day.	Side Effects.
Carbamacepine	15-30	600 – 2000 mg divided into up to 4 doses a day.	Skin rash, if allergic to carbamazepine. Diplopia (double vision), ataxia (unsteadiness) and nausea may occur initially or if the dose is too high.
Clobazam	0,1-0,2	20 - 50 mg divided into 1 or 2 doses a day.	Drowsiness may occur but this drug is less sedating than clonazepam or diazepam. Tolerance may develop.
Clonazepam	0,5-0,8	1 – 4 mg divided into 2 doses a day.	Drowsiness and sedation are quite common but these may wear off.
Ethosuximide	20-35	750 – 1500 mg divided into 2 or 3 doses a day.	Nausea and drowsiness may occur initially or if the dose is too high. Anorexia (weight loss).
Gabapentine	30	1800 – 3600 mg divided into 3 doses a day.	Drowsiness, dizziness, and headache
Levetiracetam	20-60	1000 – 3000 mg divided into 2 doses a day.	Dizziness, drowsiness, irritability, behavioural problems, insomnia, ataxia (unsteadiness), tremor, headache, nausea may occur in high dosages or when doses are increased, but will usually disappear after a few days.
Lamotrigine	5-15 1-5 + VPA	100 - 200mg if taken alone or if also taking sodium valproate. 200 – 400 mg if also taking phenytoin ,	Skin rash if allergic to lamotrigine. Drowsiness, diplopia (double vision), dizziness, headache,

AEDs	Childrens Dose mg/kg/d	Adults Dose mg/day.	Side Effects.
		phenobarbitone or carbamazepine.	insomnia, tremor and flu-like symptoms.
Oxcarbamazepine	15-30	1200 - 2400mg divided into 2 or 3 doses a day.	Skin rash, if allergic to oxcarbazepine. Diplopia (double vision), ataxia (unsteadiness), headache, nausea, confusion and vomiting.
Phenobarbital	3-5	30 – 180 mg divided into 2 doses a day.	Drowsiness may occur initially. Lethargy, sedation and slowing of mental performance may be long-lasting.
Phenytoin	5-10	150 – 600 mg divided into 1 or 2 doses a day.	Skin rash if allergic to phenytoin. Drowsiness, ataxia (unsteadiness) and slurred speech may occur if the dose is too high. Coarsening of facial features, overgrowth of gums, excess hair growth and acne may occur with prolonged therapy (over many years), as can some anaemias.
Topiramate	5-9	Up to 400 mg daily if taken alone. Usually 200 – 400 mg daily if taken with other anti-epileptic drugs, up to 800 mg.	Headache, drowsiness, dizziness, paraesthesia (pins and needles in hands and feet), loss of weight, and kidney stones. Speech disorder, impaired memory and concentration may occur when dose is increased

AEDs	Childrens Dose mg/kg/d	Adults Dose mg/day.	Side Effects.
			but will usually disappear after a few days.
Sodium valproate	20-50	400 – 2000 mg divided into 1 or 2 doses a day.	Drowsiness and tremor are infrequent side effects. Hair loss occurs in some people but is not usually severe and is usually reversible if the dose is reduced. Weight gain may occur. Liver. damage is rare. Sodium valproate has been associated with increased incidence of Polycystic Ovary Syndrome and menstrual irregularitiesthan other AEDs, if taken in pregnancy.
Vigabatrine	50-200	1000 – 4000 mg divided into 1 or 2 doses a day.	Drowsiness, behaviour and mood changes. Psychotic reactions have been reported. Visual field defects have been reported in one in three people taking vigabatrin in the long term.
Zonizamide	4-8	300 - 500mg divided into 1 or 2 doses a day.	Skin rash if allergic to zonisamide. Drowsiness, dizziness, weight loss, kidney stones, confusion, cognitive slowing, agitation, irritability, depression,

Table 5. AEDs, dose in children and adults. Side effects.

6. Conclusions

The findings of the last decade regarding the significant percentage of children with DS and epilepsy (approximately 1 in 10) highlight the importance of the awareness that physicians should start developing about this association so that they can intervene as early as possible when seizures are suspected, to maximize the patient's development and improve quality of life as much as possible.

The diagnosis, classification and treatment of epilepsy in DS must follow the guidelines applied to the general population.

Children with DS have a greater predisposition to epilepsy (specifically to West Syndrome and infantile spasms) attributed to structural and molecular abnormalities. In contrast, in adults with DS, epilepsy is associated with the accumulation of amyloid-β, due to the expression of APP that is observed in DS patients with early-onset Alzheimer-like dementia.

The prognosis of patients with DS and epilepsy will depend on several factors: type of epilepsy, age of initiation, etiology, early diagnosis and treatment's response. Epilepsy in patients with DS, as well as in the general population, in most cases represents an alteration of brain function that can be detrimental to neurological development; this produces a great amount of anxiety and concern in their parents and relatives. For this reason, all of the prognostic factors must be carefully taken into account when considering each individual case. The disease, its control and its management should be discussed in a clear and simple way with the family.

7. Acknowledgments

We would like to express our gratitude to all the patients with DS and their families; to the Library's department of the Fundació Catalana Sindrome de Down whom have made a good work in the translation of this chapter; to the members of the Epilepsy Unit from the Neurolgy Service of Sant Joan de Dèu's Hospital and to our families for their support and time.

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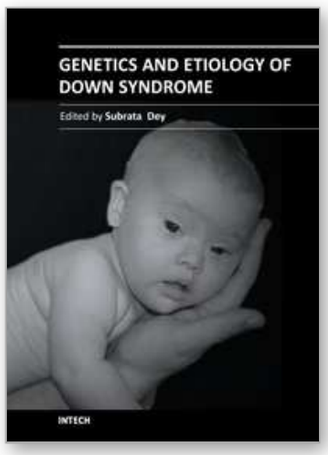

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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