Review article

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Epilepsy in children with Down syndrome

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ABSTRACT – This review discusses the various aspects of epilepsy in Down syndrome (DS) from the perspective of paediatric neurology. DS is the most common genetic cause of mental retardation (MR) with a reported prevalence of epilepsy of 1-13%. Infantile spasms (IS) or West syndrome (WS) is the most frequent epilepsy syndrome in children with DS. IS occur in 0.6-13% of children with DS, representing 4.5-47% of seizures in these children. Curiously, these patients have electroencephalographic (EEG) characteristics of idiopathic rather than symptomatic WS. Despite a lack of consensus on therapeutic approach, no significant difference has been reported among the different regimens with regards to achieving clinical remission or EEG normalisation. It appears that DS patients have better seizure control compared to other patients with symptomatic IS, and early initiation of appropriate treatment may contribute to the prevention of late seizure development and better developmental outcome. Lennox-Gastaut syndrome (LGS) also exhibits some distinctive features in children with DS including later onset and high incidence of reflex seizures. Other seizure types including partial and generalised tonic clonic seizures have also been described in children with DS. There is a high rate of EEG abnormalities in children with DS, even among children without epilepsy, however, no patterns specific to DS have been identified and EEG does not correlate with outcome. Various cellular and molecular mechanisms contribute to epileptogenesis in DS and offer an interesting field of study.

Key words: epilepsy, Down syndrome, infantile spasms, reflex seizures

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This review discusses various aspects of epilepsy in children with Down syndrome (DS). It attempts to summarise the literature on demographic characteristics, seizure type, epilepsy syndromes and aetiopathogenesis of epilepsy in DS, primarily from a clinical, paediatric, and neurological perspective. Issues of interest to adult neurologists, *e.g.* interaction between Alzheimer's dementia and epilepsy in DS or details of those investigative modalities in which the authors lack personal experience *e.g.* quantitative electroencephalography (EEG), are not discussed *(table 1)*.

Demography

DS is the most common genetic cause of mental retardation (MR), with an estimated frequency of one in 650-1000 births. Although seizures were not mentioned in the original description of DS, the prevalence of epilepsy in children with DS is now known to be higher than in the general population, but lower than in patients with MR (Goldberg-Stern *et al*., 2001; Smigielska-Kuzia *et al*., 2009). A review of studies on epilepsy in DS up to 1986, including clinic-based and institutional populations of DS (from neonates to elderly patients up to the age of 74 years), found the prevalence of epilepsy to be 0-13% with a median of 5.5% (Stafstrom *et al*., 1991).

There is a paucity of community-based prevalence data for epilepsy in DS. A registry-based study from a county in Denmark with a population of 0.61 million, found the prevalence of epilepsy in individuals with DS to be 17% (Johannsen *et al*., 1996). In Eastern countries, there is a significant difference in estimates of prevalence of epilepsy in children with DS. Studies from Japan (n=844, age <15 years) and China (n=124) have reported rates of 1.4% and 1.6%, respectively, similar to the prevalence of epilepsy in the general population (Thiel and Fowkes, 2004).

Age is an important determinant of the prevalence of epilepsy in any cohort with DS. A tri-phasic distribution of epilepsy in DS is now generally accepted and includes: infancy epilepsy, early adulthood epilepsy, and a distinct epilepsy syndrome in patients over 50-55 years (Johannsen *et al*., 1996; Moller *et al*., 2002). Seizure onset is reported to occur within a year of birth for 40% of epileptic individuals with DS and in the third decade of life for another 40% (Menendez, 2005). In the younger age group, primarily infantile spasms (IS) and tonic-clonic seizures with myoclonus are observed. However, older patients often have simple or complex partial seizures (CPS) as well as tonic-clonic seizures. A new syndrome of late onset myoclonic epilepsy in DS (LOMEDS) has been recognized; this syndrome is expected to be better delineated in the future as the life expectancy of DS patients increases (Menendez, 2005).

Sex distribution for epilepsy in children with DS has not been uniformly reported. In studies which included different seizure types, males were reported to have a younger age at onset (Goldberg-Stern *et al*., 2001). This impression is likely to be confounded by the significant male predominance in the IS group. Maternal age has also not been sufficiently reported and its relationship with incidence of epilepsy in DS remains unexplored.

Table 1. Search strategy and reference base for present review.

Electronic	
Database (vendor)	Medline (Pubmed)
Search strings	"Down Syndrome"[Mesh] AND "Epilepsy"[Mesh] "Down Syndrome"[Mesh] AND ("Epilepsy, Reflex"[Mesh] OR "Epilepsy, Tonic-Clonic"[Mesh] OR "Epilepsy, Generalized"[Mesh] OR "Epilepsy, Complex Partial"[Mesh] OR "Epilepsy, Temporal Lobe"[Mesh] OR "Epilepsy, Partial, Motor"[Mesh] OR "Epilepsy, Partial, Sensory"[Mesh] OR "Epilepsies, Myoclonic"[Mesh] OR "Epilepsies, Partial"[Mesh] OR "Myoclonic Epilepsies, Progressive"[Mesh])
Filters	Language: English Age: All Child 0-18 years
Period	1960-2009
Manual	Electronically identified articles for relevance References cited in relevant electronically identified articles
Expert opinion	Including standard text-books

Infantile spasms

Infantile spasms (IS) is the most important type of seizures in children with DS. Onset is usually at six to eight months of age (range 4-18 months) (Eisermann *et al*., 2003; Goldberg-Stern *et al*., 2001; Nabbout *et al*., 2001; Pollack *et al*., 1978; Silva *et al*., 1996; Stafstrom and Konkol, 1994; Wolcott and Chun, 1973), with male preponderance (male:female; 9:8:8:1) (Goldberg-Stern *et al*., 2001; Stafstrom and Konkol, 1994).

Clinical considerations

IS in children with DS may be attributed to other secondary lesions *e.g*. hypoxic encephalopathy due to congenital heart disease surgery or perinatal asphyxia (symptomatic), or may lack any other identifiable structural lesion of the brain (cryptogenic). Various risk factors which have been identified include prematurity (Goldberg-Stern *et al*., 2001), congenital heart disease, cardiac surgery, perinatal hypoxia-ischaemia and vaccine encephalopathy (Stafstrom and Konkol,

1994). The family history of DS (Stafstrom and Konkol, 1994) and of other epilepsies (Eisermann *et al*., 2003) probably also contribute. Most children with DS-IS have trisomy 21 although cases with mosaicism or translocation have been documented (Pollack *et al*., 1978; Silva *et al*., 1996; Stafstrom and Konkol, 1994). A detailed study of EEG characteristics has emphasised three important features in children with cryptogenic DS-IS (Silva *et al*., 1996):

– symmetrical hypsarrhythmia;
– no focus uncovered by intravenous diazepam;
– single rather than clustered spasms on ictal EEG.

Children with symptomatic DS-IS have the following distinguishing features:

– no interictal paroxysmal activity between consecutive spasms;
– electrographic seizure initiated by or combined with focal discharge(s).

Based on these characteristics, DS-IS is arguably associated with EEG attributes of idiopathic WS. Moreover, when other types of seizures occur subsequently, they are not suggestive of symptomatic epileptic encephalopathy but rather of age-related idiopathic generalised epilepsy which resolves after a few months or years (Silva *et al*., 1996).

Other investigators have also reported classic hypsarrhythmia as the commonest EEG pattern in DS-IS (Eisermann *et al*., 2003; Pollack *et al*., 1978). However, focal discharges, hypsarrhythmia variants, burst suppression patterns and hemi-hypsarrhythmia in the absence of structural correlate have also been documented (Goldberg-Stern *et al*., 2001; Stafstrom and Konkol, 1994).

There is a paucity of neuroimaging data of children with DS-IS primarily because many of these studies were conducted before the widespread availability of imaging modalities. It is therefore expected that symptomatic groups show characteristic lesions. Regarding cryptogenic DS-IS, most of the available evidence shows normal imaging, however, occasional cases with mild atrophy have been described (Eisermann *et al*., 2003; Silva *et al*., 1996).

An important concern is the effect of spasms on developmental milestones. The available data shows that there is regression of developmental skills with onset of spasms in an age-dependent manner; onset after infancy is associated with a less detrimental effect and partial restoration of development with the cessation of spasms (Goldberg-Stern *et al*., 2001; Silva *et al*., 1996).

Therapy and outcome

Treatment of DS-IS is fraught with a lack of uniformity of drug choice, dose, duration or other regimen. Goldberg-Stern *et al*. (2001) reported that two of their nine patients responded to adrenocorticotrophic hormone (ACTH) monotherapy (20-25 units/m^2/day), five responded to sodium valproate (VPA) monotherapy (30 mg/kg/day) and two responded to therapy with ACTH followed by VPA. Silva *et al*. (1996) reported two patients with vigabatrin (VGB) monotherapy (100 mg/kg/day), two with VPA (40 mg/kg/day) monotherapy, and one with high dose pyridoxine (750 mg/day). In addition, ten patients received hydrocortisone, at 15 mg/kg/day for two weeks, followed by tapering over the subsequent two weeks. Nabbout *et al*. (2001) also described treatment with VGB (75-100 mg/kg/day) in four patients, with a cessation of spasms within two weeks and early discontinuation after six months. Other drugs used for controlling spasms in children with DS have included phenobarbitone, clonazepam, diazepam, phenytoin and primidone (Pollack *et al*., 1978; Wolcott and Chun, 1973).

These treatment differences represent, among other things, the treatment options available and the prevailing therapeutic rationale at a given time. The definition of treatment response has been fairly uniform and has included clinical spasm cessation and EEG normalization. However, the period of time chosen for assessment has varied from two to six weeks. Overall, no significant difference has been reported among the different therapeutic regimens with regards to achieving clinical remission or EEG normalization (Goldberg-Stern *et al*., 2001; Silva *et al*., 1996). EEG features have not been shown to predict response to treatment.

The long-term developmental outcome in children with DS-IS is of particular importance. It should be recognised that developmental assessment presents unique problems in this subset of children, who may have preexisting developmental problems either due to DS itself or co-morbidities, such as hypoxic-ischaemic brain injury. Moreover, the developmental norms for children with DS are not well-delineated. This makes it difficult to assess whether any arrest or regression is attributable to epilepsy. One important predictor of developmental outcome in such children is the starting time of appropriate therapy for IS. Eiserman *et al*. (2003) found that there was a statistically significant correlation between treatment lag and time of cessation of spasms (R=0.55, p=0.02), developmental quotient (R=-0.75, p=0.003), and a score of autistic features (R=0.57, p=0.04). A treatment lag of more than two months predicted the persistence of seizures. Moreover, it was found that a delayed response to treatment also predicted a lower developmental quotient and higher score of autistic features. Whereas some investigators have found that

milestones were regained after appropriate IS therapy (Silva *et al*., 1996; Stafstrom and Konkol, 1994), all five children reported by Goldberg-Stern *et al*. (2001) continued to be moderately to severely retarded, along with autistic features and a lack of language skills, despite seizure remission. Further longitudinal studies are required to clarify these issues.

The development of other seizure types or epilepsy syndromes in children with DS-IS is another relevant outcome issue. Various other seizure types have been documented during follow-up in cohorts of DS-IS including focal, myoclonic, generalised tonic-clonic and atonic seizures (Goldberg-Stern *et al*., 2001; Silva *et al*., 1996). Progression to Lennox-Gastaut syndrome has been documented infrequently, relative to other groups of WS (Stafstrom and Konkol, 1994). Mostly, these seizures have been shown to respond to conventional medications including VPA and benzodiazepines. Compared to other causes of symptomatic WS, it would appear that DS patients have relatively better prognosis with regards to seizure control (Menendez, 2005).

Pathophysiology of DS-IS

In order to study the biology and clinical characteristics of DS-IS, a need for a valid animal model has long been felt. The most widely studied animal model of DS is the Ts(17^{16})65Dn (Ts65Dn) mouse. This mutant mouse is segmentally trisomic for the distal end of murine chromosome 16. However, seizures have not been reported to date in this mutant mutation. Recently, the Ts65Dn mouse was reported to over-express the G-protein-coupled inward-rectifying potassium channel subunit 2 (GIRK2) due to the extra gene copy of the *KCNJ6* (GIRK2*)* gene located within triplicated segments of mouse chromosome 16. In addition, a significant increase in GABA-B receptor-mediated GIRK current was observed in primary hippocampal neurons prepared from Ts65Dn mice (Cortez *et al*., 2009). GABA-B receptor agonists are known to induce a unique constellation of seizures in rodents. Hence, it was reasoned that the Ts65Dn mouse might be uniquely sensitive to the seizure-inducing propensity of GABA-B receptor agonists.

Indeed, it was found that the naïve Ts65Dn mice, with spontaneous spike-and-wave discharges, worsened with baclofen and γ-butyrolactone[1] (GBL), which induced acute epileptic extensor spasms (AEES) associated with epileptiform polyspike bursts and an electro-decremental response on EEG. Moreover, GABA-B agonist-induced AEES were significantly reduced with VGB, rodent ACTH fragment, VPA and ethosuximide (ESM). In addition, the AEES and EEG worsened with baclofen and 5-hydroxy tryptophan.

These findings are important for two reasons. First, they show that the GABA-B agonist-treated Ts65Dn mouse demonstrates the unique clinical, electrographic, and pharmacological signature of IS and in general represents a valid model for IS, in particular, for DS-IS. Secondly, they also provide insight into the pathogenesis of this disorder. The overexpression of GABA-B receptor in the Ts65Dn mouse brainstem and thalamus, the exacerbation of clinical and EEG seizures by GABA-B agonists, and the suppression of GBL-induced spasms in the Ts65Dn mouse by ESM support the involvement of brainstem and thalamo-cortical circuits and GABA-ergic mechanisms in the generation of IS. VGB markedly exacerbates GABA-B agonist-induced absence in normal rodents, but has the opposite effect in the Ts65Dn mouse, providing additional evidence that thalamo-cortical GABA-mediated mechanisms may be involved in this phenomenon. However, the data regarding the specific age at which these mechanisms occur, relevant information for any model of IS, remains open to further investigation (Cortez *et al*., 2009).

Lennox-Gastaut syndrome (LGS)

A review of data from five epilepsy centres over 30 years identified 13 DS patients (eight males, five females) with LGS (Ferlazzo *et al*., 2009). Surprisingly, in none of the cases did WS precede the onset of LGS. The mean age at onset was 9.1 years (range 5-16) and 62% of the patients experienced seizure onset after eight years of age. A marked predominance of reflex seizures, precipitated by sudden unexpected sensory stimulation, was documented preceding or accompanying the LGS phenotype. Common sensory triggers leading to seizure precipitation included mainly noise and touch, contact of water with the face, contact of a glass with the mouth, emotions or going upstairs. The reflex seizure types were tonic, atypical absence, myoclonic, generalised tonic-clonic and drop attacks. The majority of patients had normal neuroimaging. Most of the patients were refractory to medical treatment.

Reflex seizures

As discussed above, reflex seizures occur commonly in DS-related LGS. However, they have also been frequently documented in children with DS *per se*. A common feature is the fact that seizures are startle-induced, but otherwise occur in different contexts in

[1] GBL is a prodrug for the known GABA-B agonist γ-hydroxybutyrate (GHB). The inactive GBL is converted to GHB by a circulating lactonase.

different patients mostly with symptomatic epilepsy. Usually, in any one patient, reflex seizures are stereotyped in semiology. The age of onset ranges from 2.5-24 years (Guerrini *et al*., 1990) and some important features, which distinguish DS-related reflex seizures from those occurring in other contexts, have been defined (Guerrini *et al*., 1990). Reflex seizures are usually detected after several years of spontaneous seizures, which is not the case for DS patients. Moreover, DS-related reflex seizures occur in the absence of spasticity or focal motor deficits, but have otherwise been described in children with cerebral palsy and structural brain lesions.

Miscellaneous seizure types

Many investigators have collected data on various seizure types or epilepsy syndromes which occur in DS (Goldberg-Stern *et al*., 2001; Johannsen *et al*., 1996; Smigielska-Kuzia *et al*., 2009). These studies are very heterogenous in terms of study population, purpose, design, extent of aetiologic work up and outcome. Seizure types documented in children with DS have included CPS with or without secondary generalisation, primary generalised seizures and unclassifiable seizures. A child with gelastic features has also been described who evolved with typical flexor spasms (Pollack *et al*., 1978).

Surprisingly, many reports have either failed to comment on, or include, children with febrile seizures. Some of the seizures resulted from definable causes such as stroke or hypoxic-ischaemic encephalopathy. In rare cases, other genetic causes have been documented to co-exist and include phenylketonuria and neurofibromatosis-1 (Goldberg-Stern *et al*., 2001). A targeted approach to identify the aetiology of seizures in DS was made by Stafstrom *et al*. (1991). A symptomatic basis could be demonstrated in 61% of their patients. Additional causes identified included: bacterial and viral neurological infections, cerebrovascular disease including moya-moya syndrome, intracranial bleed and chemotherapy related neurotoxicity.

A high prevalence of EEG abnormalities (20-25%) in DS has been recognized even in the absence of seizures (Ellingson *et al*., 1973). Despite this, no distinctive EEG pattern or correlation with behavioural phenotype has been recognized.

To better interpret data from previous reports, it is pertinent to consider some of the design and conduct issues in these studies. The operational definition of epilepsy (one or less unprovoked seizure) was not specified, cytogenetic or neuroimaging break up of cases was not provided, and finally, both seizure types and epilepsy syndromes were not distinguished (Goldberg-Stern *et al*., 2001; Smigielska-Kuzia *et al*., 2009). In a recent review (Menendez, 2005), about 8% patients with DS were shown to have a seizure disorder, of which 47% developed partial seizures, 32% infantile spasms and 21% generalised tonic-clonic seizures.

Epileptogenesis in Down syndrome

Seizure susceptibility in patients with DS is attributable both to inherent genetic differences in brain structure and to secondary complications. On a macroscopic level, neuroimaging has delineated certain brain differences between patients with DS and the general population. In a study of children with DS, compared to age-matched controls, hippocampal volumes were found to be significantly smaller in the DS group even when corrected for overall brain volume. Another study has shown a disproportionately smaller cerebellar volume (Menendez, 2005). The pathogenic significance of these findings has not been defined.

Any abnormality that enhances net excitation or limits net inhibition would favour the development of a hyper-excitable, seizure-prone state. Down syndrome brains are characterized by a 20-50% decrease in the number of small granule cells, lower neuronal density and abnormal neuronal distribution, especially in cortical layers II and IV. These granule cells are inhibitory, gamma-amino-butyric acid (GABA)-containing cortical inter-neurons. A decrease in such cells, secondary to a defect in neurogenesis or neuronal migration, would shift the balance in favour of net cortical excitation. Another consistent microscopic finding in DS is dysgenesis of dendritic spines. In addition to reduced number, those present tend to be longer and have thinner spine necks. This spine morphology is common in normal brains prenatally, but after birth spine morphology becomes more varied. However, in DS, long-necked primitive dendritic spines persist after birth, suggesting a dysgenetic process or trans-synaptic degeneration. Functionally, these morphological abnormalities will distort synaptic input such that voltage attenuation is greater in spines with short, thick necks. Neuronal membranes in DS are abnormally hyper-excitable. Cultured dorsal-root ganglion neurons from DS foetuses have been shown to display several hyper-excitable membrane properties, including decreased action potential after-hyperpolarizations and decreased voltage thresholds for action potential generation. These changes can be explained by alterations in membrane ion channels. Similar results were obtained in mice with trisomy 16, an experimental model for DS, with which a rapid spike rise and fall was recorded from the dorsal root ganglia neurons.

Table 2. Putative mechanisms of epileptogenesis in Down syndrome.

Neuronal or synaptic anatomy
- Fewer inhibitory inter-neurons - Decreased neuronal density - Abnormal neuronal lamination - Persistence of dendrites with foetal morphology - Primitive synaptic profiles
Membrane channel dysfunction - Altered membrane potassium permeability - Decreased voltage threshold for spike generation - Smaller hyperpolarization following spikes - Altered action potential duration

Another putative mechanism involves anomalous glutamate receptor function. The level of this excitatory transmitter is elevated in both DS and IS. Furthermore, the gene for at least one glutamate receptor subunit is localized to the DS region on the distal arm of chromosome 21 (Stafstrom and Konkol, 1994).

Hence, the available evidence suggests interplay between pathologically hyper-excitable membrane properties (ion conductances), altered neuronal structure (dendritic spines, synaptic density), disproportionately fewer inhibitory inter-neurons and altered neuro-transmitter receptor function (*table 2*). How these abnormalities are regulated by an additional chromosome 21 remains to be determined (Stafstrom, 1993; Stafstrom *et al*., 1991).

Recently, some nutritional similarities between epilepsy and DS with pathogenic significance were reported (Thiel and Fowkes, 2004). Uncontrolled data from human and animal studies has led to the identification of altered levels of several nutrients including vitamins, trace metals and amino acids. It has been proposed that these alterations may affect neurotransmitter levels or function, however, these observations should be further substantiated before any conclusions can be made.

Conclusion

Epilepsy is a common co-morbidity in children with DS and has an age dependent prevalence. IS represents the most important epilepsy syndrome in DS patients and differs from other symptomatic causes of WS. DS-related reflex seizures are probably a unique seizure type, although no EEG features of epileptiform activity are specific to DS. In general, for DS patients with epilepsy, a good therapeutic response is expected with conventional antiepileptic drugs. Finally, various mechanisms contribute to epileptogenesis in DS and offer an interesting field of study. □

Disclosure

None of the authors has any conflict of interest or financial support to disclose.

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