Doose syndrome (myoclonic–astatic epilepsy): 40 years of progress

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PUBLICATION DATA
Accepted for publication 8th June 2010.
Published online.

LIST OF ABBREVIATION
LGS Lennox–Gastaut syndrome

Doose syndrome, otherwise traditionally known as myoclonic–astatic epilepsy, was first described as a unique epilepsy syndrome by Dr Hermann Doose in 1970. In 1989, the International League Against Epilepsy classified it formally as a symptomatic generalized epilepsy, and 20 years later it was renamed 'epilepsy with myoclonic–atonic seizures'. In this review, we discuss the components of this unique disorder including its incidence, clinical features, and electroencephalographic findings. Recent evidence has suggested possible genetic links to the GEFS+ (generalized epilepsy with febrile seizures plus) family, and, additionally, some children with structural brain lesions can mimic the Doose syndrome phenotype. Treatment strategies such as corticosteroids, ethosuximide, and valproate have been described as only partially effective, but newer anticonvulsants, such as levetiracetam and zonisamide, may provide additional seizure control. The most effective treatment reported to date appears to be the ketogenic diet. Prognosis is quite varied in this disorder; however, many children can have a remarkably normal neurodevelopmental outcome.

Forty years ago, Dr Hermann Doose from Germany, first described the features of a previously incompletely defined epilepsy syndrome that he referred to as 'centrencephalic myoclonic–astatic petit mal'. This syndrome is typically known as myoclonic–astatic epilepsy, although it has recently been redefined by the International League Against Epilepsy as 'epilepsy with myoclonic–atonic seizures'. However, many neurologists and parents continue to refer to this condition as Doose syndrome. Since its first description in 1970, knowledge of Doose syndrome and its genetic background has continued to grow. Concurrently, research into the efficacy of multiple treatments, both pharmacological and dietary, has greatly expanded.

HISTORY

The first atonic seizures were described by Hunt in 1922. When they were accompanied by absence or myoclonic seizures, they were grouped under the term 'petit mal'.[1] For the next 40 years, children with various combinations of atonic, myoclonic, and absence seizures were typically grouped together and diagnosed as having 'petit mal' epilepsy until there grew a greater recognition of Lennox–Gastaut syndrome (LGS).[2] The concept of separating myoclonic seizures from LGS first emerged in the 1960s. In 1968, Krause[3] described myoclonic and atonic seizures, but it is likely that several different epilepsy syndromes (including LGS and myoclonic absence seizures) were grouped together under one definition.

Myoclonic–astatic epilepsy was first clearly described as an independent epilepsy syndrome by Dr Hermann Doose[4] in 1970. In his original paper, Doose reported 51 children with the now traditional clinical semiology and electroencephalographic pattern were described. In 1989, the International League Against Epilepsy recognized myoclonic–astatic epilepsy as one of the symptomatic generalized epilepsies and laid down criteria for its diagnosis (Table I). A recent revision by the International League Against Epilepsy in 2010 renamed myoclonic–astatic epilepsy as 'epilepsy with myoclonic–atonic seizures', and classified it as 1 of the 11 childhood-onset 'electroclinical syndromes'.[5]

In his initial case series, Doose[4] described Doose syndrome as a primary generalized idiopathic seizure disorder that included multiple different seizure types, of which myoclonic and astatic seizures were the most prominent. The electroencephalogram (EEG) usually reveals synchronous spike and wave activity with abnormal background theta, although most of the background could be quite normal for age. He recognized the progression of Doose syndrome in some instances to cognitive impairment and also noticed a high rate of seizures among immediate family members.

Doose syndrome is relatively common, with an incidence of about 1 in 10 000 children, constituting approximately 1 to 2% of childhood-onset epilepsies. It is more common in males, except when onset is in the first year of life, when the incidence is equal in both genders. In 94% of cases, onset occurs within the first 5 years of life, usually between 3 and 4 years of age, but 24% of children experience their first seizure in the first year of life.[6] However, further seizures may not occur for some time, which can delay the diagnosis of myoclonic–astatic epilepsy. Conversely, some children may present with frequent explosive-onset seizures, with multiple

Table I: Myoclonic-astatic epilepsy as defined by the International League Against Epilepsy (1989)[7]

Normal development until onset of seizures
No organic or other obvious cause for seizures
Onset of myoclonic–astatic seizures between 7mo and 6y
Ratio of males to females = 2:1, except in first year of life (1:1)
Often a hereditary predisposition
Seizure types: myoclonic, astatic, myoclonic–astatic, absence, tonic, clonic, generalized tonic–clonic
Status epilepticus is common
Electroencephalogram is initially normal (or background theta), then generalized polyspike and wave epileptiform activity is noted
Not consistent with Dravet syndrome, Lennox–Gastaut syndrome, or benign myoclonic epilepsy

semiologies at the time of first presentation. In individuals in whom the first seizure after 4 years of age, the initial manifestation is more likely to be absence seizures.

In 1989, the International League Against Epilepsy allocated Doose syndrome to the category of cryptogenic or symptomatic seizures and defined it as having no organic cause and associated with no other form of myoclonic epilepsy, presenting between the age of 7 months and 6 years following previously normal development, and characterized by a generalized EEG findings with 2 to 3Hz activity and no focal discharges.[7] The category under which Doose syndrome is classified is debated, and many authors, including Doose himself, thought that it may be an idiopathic disorder with a genetic predisposition. However, there have been reports of children with Doose syndrome who have identified underlying abnormalities, and thus symptomatic–structural aetiologies to explain the phenotype. There have been reports of individuals with Sturge–Weber syndrome in whom EEG findings are typical of Doose syndrome.[8] Usually, however, magnetic resonance imaging findings in children with Doose syndrome, when they are obtained, are normal. In one case report,[8] Doose syndrome was thought to have been triggered by a partially acting anticonvulsant (oxcarbazepine), and subsequently resolved when the child was switched to valproate. Underlying genetic disorders are in the process of being discovered and may shift our understanding of Doose syndrome to one of a symptomatic genetic epilepsy. One possible theory is that a symptomatic cause (be it structural or genetic) that would normally cause partial seizures is secondarily generalized for an unknown reason (at times temporarily) with characteristic myoclonic and astatic seizures. In the 2010 reclassification, Doose syndrome is listed as an epileptic encephalopathy because of the effects of seizures on cognition, and thus is in the same category as Landau–Kleffner syndrome and LGS.

CLINICAL FEATURES

Doose syndrome is associated with multiple different seizure types. Myoclonic seizures consist in quick jerking movements that can occur truncally or axially. If they occur truncally, they may constitute a myoclonic drop in which the individual appears to be forcefully thrown to the floor. Smaller jerks may be only subjectively perceived by the child or may consist in subtle vocalizations. Astatic or atonic seizures may occur, causing the individual to lose tone briefly, leading to the appearance of head nodding; typically, however, the child will quickly regain balance and will not completely fall. In our experience, although parents frequently buy helmets as a safety measure, they are rarely necessary. Astatic seizures are often preceded by myoclonus. Axial tonic seizures and tonic vibrating seizures may also occur later in the course of the disease.

Over time, seizures occur more often in the early hours of the morning during sleep than during the day. All seizure types can result in status epilepticus, including non-convulsive status epilepticus, previously called 'status of minor seizures', as well as myoclonic and absence status epilepticus.

What this paper adds

- Doose syndrome is one of the unique childhood-onset epilepsy syndromes, with characteristic clinical and electroencephalographic features.
- In recent years, genetic and structural aetiologies have been identified as potentially causative.
- Despite the frequent seizures, cognitive outcomes can be surprisingly good.
- Many anticonvulsant treatments have been reported to be helpful, but the ketogenic diet is probably the most likely to lead to freedom from seizures.

EEG FINDINGS

The EEG may be initially normal, and with progression of the disease will demonstrate brief bursts of 2 to 5Hz spike and wave and polyspike and wave complexes (Fig. 1). There may be background slowing, and parietal theta has been described. This abnormal background and spike–wave activity may remain even after clinical remission has occurred – often during sleep. However, what is quite remarkable is the overall generally normal posterior background rhythms and sleep architecture of children. This can help to distinguish children with Doose syndrome from those with LGS, in whom the EEG is much more abnormal with little to no normal background activity and slower (2–2.5Hz) spike–wave runs for prolonged periods. Occipital 4Hz activity may also be seen, and can be attenuated by eye opening. Oguni et al.[9] found that, during atonic seizures, the greater the intensity of the seizure, the more positive was the second component of the spike–wave. Photosensitivity with 4-7Hz spike–wave complexes may be also seen, as well as 3Hz spike–waves, which can be characteristic of typical childhood absence epilepsy. Although Doose syndrome is thought to be a generalized seizure disorder, it is possible to see pseudofoci of activity on the EEG, which may shift in laterality.

In younger individuals, the EEG may show continuous irregular activity which looks similar to hypsarrhythmia. During status epilepticus, rhythms consisting of continuous spike–wave activity with interposed slow waves can be seen. This type of activity can lead to clinically unpredictable myoclonus occurring in multiple parts of the individual's body.

DIFFERENTIAL DIAGNOSIS

The seizure types that are most difficult to separate from Doose syndrome are benign myoclonic epilepsy, severe myoclonic epilepsy, atypical benign partial epilepsy of childhood, and LGS. Severe myoclonic epilepsy or Dravet syn-

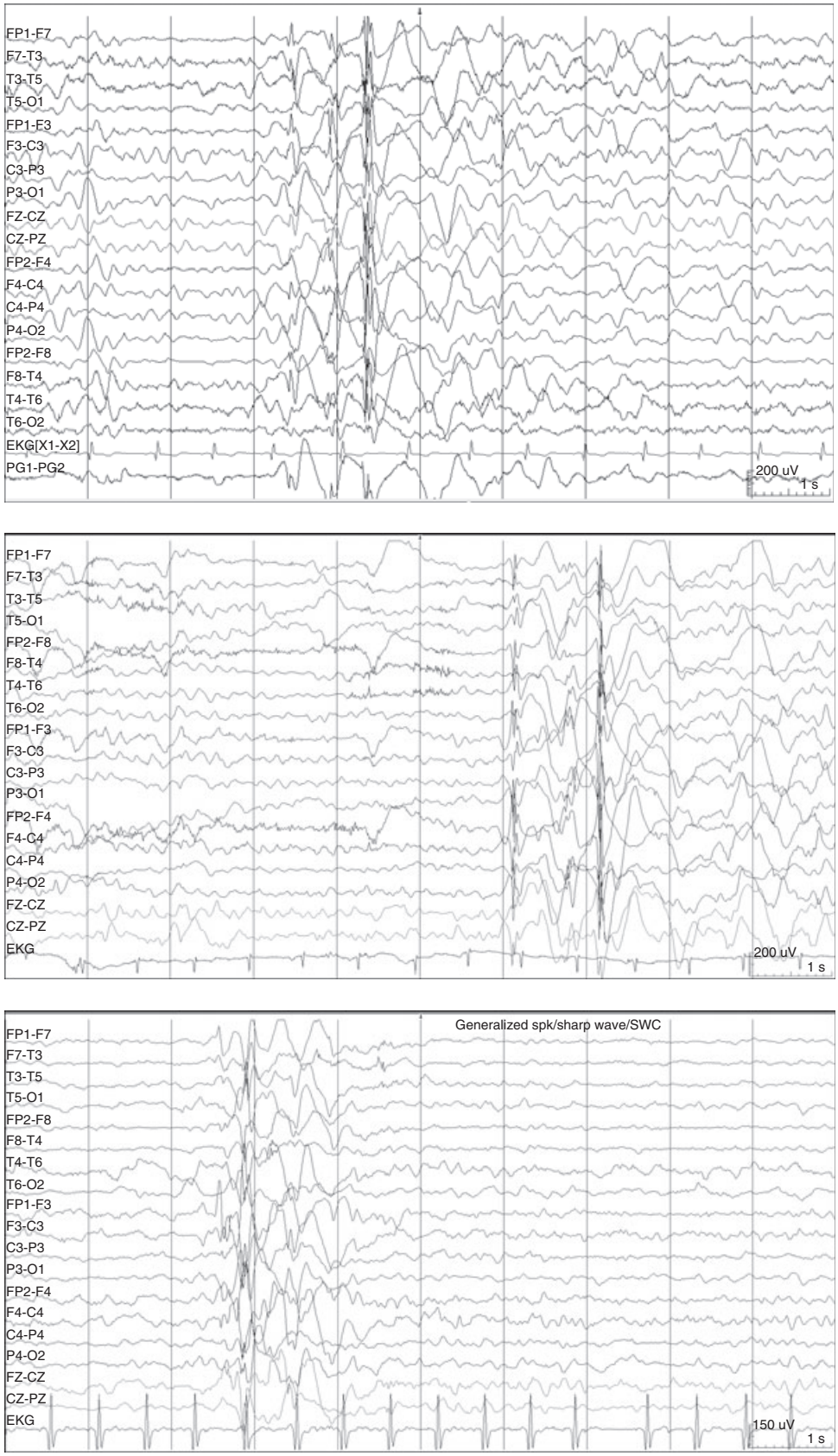

Figure 1: Electroencephalogram (EEG) findings in Doose syndrome. Three different children affected, with nearly identical EEGs demonstrating bursts of spike–wave activity superimposed on an otherwise normal background.

Table II: Anticonvulsant therapies reported in the treatment of Doose syndrome

Anticonvulsant therapy	Years reported	No. of individuals	50–99% seizure reduction (%)	Seizure-free (%)
Ketogenic diet	2002[10]	26	35	58
	2006[22]	11	36	18
	2007[17]	10	–	30
Adrenocorticotrophic hormone	2002[10]	22	23	36
	2007[17]	5		0
Ethosuximide	2002[10]	34	32	32
	2007[17]	4		25
Valproic acid	1977[16]	32	25	25
	2002[10]	57	28	12
	2007[17]	19	–	11
Lamotrigine	2007[17]	11	–	18
Prednisone	2007[17]	2	–	0
Clonazepam	2002[10]	43	23	14
	2007[17]	3		0
Topiramate	2003[18]	6	66	0
	2003[27]	4	75	25
Levetiracetam	2006[21]	1	1	0
	2007[17]	13	–	23
Zonisamide	2007[17]	5	–	0

–, information unavailable.

drome is distinct from Doose syndrome. Although severe myoclonic epilepsy may begin with febrile seizures in children of normal intelligence, as does Doose syndrome, children with Dravet syndrome will often experience partial seizures and exhibit focal findings on their EEG that are not present in children with Doose syndrome. Myoclonus is prominent in severe myoclonic epilepsy, and it is rare to see an atonic component.

Both LGS and Doose syndrome are associated with multiple seizure types. Like Doose syndrome, LGS is classified by the International League Against Epilepsy as an electroclinical syndrome and an epileptic encephalopathy (previously as a symptomatic generalized epilepsy); however, magnetic resonance imaging abnormalities are more common in individuals with LGS. A high rate of seizures and EEG traits resembling those seen in Doose syndrome have also been found in the relatives of affected children.[4] In Doose syndrome, individuals have typically normal cognition before the onset of seizures (and may maintain normal cognition); however, in LGS, there is often cognitive delay from the start. Tonic seizures, although seen in both LGS and Doose syndrome, occur while awake and asleep in LGS but only infrequently during sleep in individuals with Doose syndrome. Additionally, tonic vibratory seizures and myoclonic status are rare in individuals with LGS.

EEG findings also differ in the two epilepsy syndromes. LGS is characterized by electrical status epilepticus during slow-wave sleep, whereas normal background activity is more likely in Doose syndrome. Considering all of these similarities, it is possible that the two syndromes are different manifestations of a single epilepsy syndrome, with Doose syndrome at the mild end of the spectrum and LGS at the more severe end. Some have theorized that other epilepsy syndromes may be on a spectrum of a single disorder, including, most notably, benign epilepsy with centrotemporal spikes and Landau–Kleffner syndrome. This is purely conjecture at this point.

GENETICS

Genetics plays an important role in Doose syndrome and may become an additional method for differentiating it from other disorders. Doose was the first to point out the high incidence of both seizures and similar EEG findings among the family members of affected individuals. The prevalence of abnormal EEG findings was found to be 68% among immediate family members and up to 80% if distant relatives were included.[4] Early papers reported that clinical seizures occurred in 35 to 40% of relatives of individuals with Doose syndrome.[4,10] Although the prevalence of specifically myoclonic and astatic seizures among family members was found to be only about 2%, this is 200 times higher than in the general population.[11] The most common EEG findings in family members are photosensitivity and abnormal theta background rhythm.

Multifactorial inheritance is likely in this condition. This is partly demonstrated by the fact that Doose syndrome has many different seizure manifestations. Doose described 'polygenes' that lead to different manifestations and also affect the likelihood that immediate family members will be affected. Individuals with Doose syndrome were some of the first to be diagnosed with sodium channel neuronal type 1 alpha subunit (*SCN1A*) mutations within the generalized

epilepsy with febrile seizures plus (GEFS+) disorder.[12] Individuals have also been found to have sodium channel subunit beta-1 (*SCN1B*) and gamma-aminobutyric acid receptor subunit gamma-2 (*GABRG2*) mutations.[6] A new point mutation in exon 20 of *SCN1A* has just been discovered in a family in which one brother has severe myoclonic epilepsy and one has Doose syndrome, probably inherited from a father who had one febrile seizure and a few generalized tonic–clonic seizures throughout his life.[13] However these genes have not been found consistently in sporadic cases, suggesting that these gene mutations are unlikely to be the primary cause of Doose syndrome.[14,15]

TREATMENT

Doose syndrome is historically described as difficult to treat. Multiple anticonvulsant medications as well as less traditional therapies have been reported in the literature for the treatment of Doose syndrome (Table II). One of the earliest therapies reported was corticosteroids, specifically adrenocorticotrophic hormone and high-dose dexamethasone. Doose et al. first mentioned the use of high doses of up to 1mg/kg dexamethasone or adrenocorticotrophic hormone (80IU) to control seizures.[4] Oguni et al.[9] also suggested adrenocorticotrophic hormone for refractory non-convulsive status epilepticus; pulse steroids have also been described. The major drawbacks to steroid use are seizure recurrence after discontinuation and significant side effects from long-term use. In our experience, steroids are hardly ever a worthwhile long-term solution.

Ethosuximide is reported to be one of the more effective standard anticonvulsants, especially when absence seizures are the primary seizure type. Valproic acid and lamotrigine have also been described as beneficial and even, together, synergistic in the treatment of Doose syndrome.[16,19,20] Lamotrigine, however, should probably not be used in individuals for whom myoclonic seizures are the most prominent seizure type, as it may cause paradoxical worsening. Additionally, lamotrigine must be titrated slowly to prevent rash and is less practical in the case of injurious atonic seizures. Levetiracetam and zonisamide have been anecdotally used for Doose syndrome and may be helpful. However, the use of levetiracetam has been described in only nine children in two studies, and only one child achieved freedom from seizures, and that for less than 6 months.[17,21] Information on the use of clobazam and newer anticonvulsants, such as rufinamide and lacosamide, in Doose syndrome is not available at this time.

Of importance, carbamazepine, phenytoin, and vigabatrin have all been reported to *worsen* seizures in Doose syndrome. Several authors have specifically cautioned against the use of these anticonvulsants in Doose syndrome and a dramatic worsening of seizures may, in fact, help clarify the diagnosis. Seizure remission has been reported even in the absence of changes to medication, suggesting that spontaneous remission of seizures does occur, although the incidence is unknown.

The ketogenic diet is perhaps the most widely reported therapy for Doose syndrome, and may in fact be the most efficacious. In the first description of the response of Doose syndrome to the ketogenic diet in 2002, Oguni et al.[10] reported the ketogenic diet to be effective (58% seizure-free, 35% with >50% seizure reduction, and the rest with mild improvement), even after multiple other therapies had been tried and failed. Adrenocorticotrophic hormone was the second most effective therapy in that study. Four years later, Caraballo et al.[22] also studied the ketogenic diet, with over half of those treated experiencing a reduction in seizures of more than 50%. Both groups stated in their discussion sections that the ketogenic diet should be considered first-line therapy in Doose syndrome rather than a last resort. To our knowledge, the first-line use of the ketogenic diet, although logical, has not been reported to date – although we have used it with some success, typically after one or two anticonvulsants (e.g. valproate or levetiracetam) have been tried initially.[23] The most recent, and perhaps most convincing, evidence of the benefits of the ketogenic diet for the treatment of Doose syndrome was published in 2007 by Kilaru and Bergqvist[17] from Philadelphia. In their retrospective study they demonstrated that the ketogenic diet was highly effective both clinically and electrographically. The authors went on to highlight how the ketogenic diet was the last therapy tried yet the most successful, stating the ketogenic diet 'perhaps should be considered earlier in the treatment course'.[17] As a result of this study and the others previously mentioned, the 2009 expert consensus guideline for optimal use of the ketogenic diet listed Doose syndrome as one of the eight probable indications for the ketogenic diet.[24] The vagus nerve stimulator has been tried in a single reported case without benefit.[25]

PROGNOSIS

Doose syndrome may have a favourable or unfavourable prognosis. Outcomes can range from normal cognition to severe intellectual disability and from seizure freedom to intractability. It is not usually possible to predict the outcome in the first year of disease, either clinically or from the EEG findings. However, disease progression resulting in episodes of status epilepticus, including tonic vibratory seizures and myoclonic status, as well as cognitive decline reflects an unfavourable prognosis.

Doose syndrome of unfavourable prognosis is characterized by generalized tonic–clonic seizures in the first 2 years of life, early development of myoclonic status, absence or convulsive status epilepticus, tonic seizures, persistence of the abnormal background theta rhythm, and failure to develop a background alpha rhythm. A poor prognosis is also suggested by sleep-onset seizures, as well as the development of myoclonic seizures after 4 years of age (which may indicate persistence of excitatory pathways).[26] Anecdotally, in children with a poor prognosis, cognitive impairment is accompanied by a tendency towards an intractable response to anticonvulsants and the ketogenic diet.

In their original paper, Doose et al.[4] reported that only 26% of individuals had normal cognition. In contrast, Oguni et al.[10] later reported normal intelligence in 59% of individuals, with only 20% exhibiting mild developmental delay. Similarly, Kilaru and Bergqvist[17] reported that 43% of the individuals were developmentally normal at the final evaluation and 52% exhibited mild delay. Today 80 to 90% of chil-

dren with Doose syndrome exhibit normal cognition or only minimal cognitive impairment, but it is not known whether this improvement is the result of earlier recognition and educational interventions, anticonvulsants such as valproate and levetiracetam, or, perhaps most likely, the widespread availability of the ketogenic diet.[10,17]

FUTURE DIRECTIONS

Although there has been much research into the diagnosis and treatment of Doose syndrome over the past four decades, a great deal of work remains to be done. As more genetic defects are identified with the use of comparative genome hybridization arrays, it is likely that more genetic abnormalities will be described and may answer the question as to whether Doose syndrome is a symptomatic or idiopathic disorder. Treatment studies involving the clearly efficacious ketogenic diet as a first-line therapy compared with traditional anticonvulsant therapy would be beneficial in further clarifying its particular efficacy in treatment of Doose syndrome. Exploring alternative, less restrictive forms of the ketogenic diet, such as the modified Atkins diet and low glycaemic index treatment, may make dietary treatments more accessible to larger numbers of children with Doose syndrome worldwide. At our centre, we are continuing to study the effect of long-term ketogenic dietary treatment in individuals, including those with Doose syndrome. Neuropsychological outcomes decades after diagnosis and treatment will provide further insights into the outcomes in these children.

CONCLUSIONS

Forty years ago, Hermann Doose recognized that seizures with myoclonus and atonic features were distinct from the other epilepsy syndromes that had been described with myoclonus and were categorized under the heading of 'petit mal' or LGS. Today, Doose syndrome has emerged as of particular interest because of the potential genetic causes, and because it is a unique, well-defined condition. It is especially important to recognize the strong potential for a good cognitive outcome, despite frequent troublesome daily seizures, with earlier recognition and effective treatment.

Useful websites for parents

http://www.doosesyndrome.com
http://health.groups.yahoo.com/group/doosesyndrome/
http://myoclonicastaticepilepsy.com
http://professionals.epilepsy.com/page/doose_syndrome.html

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