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Epilepsy and other comorbidities in Down syndrome

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In this article

Abstract

Down syndrome (DS) is the most common cause of intellectual disability. Due to many genetic and biochemical aberrations, people with DS suffer from several somatic disorders and concomitant diseases. Epilepsies occur more often than in the normal population, but less often than with intellectual disability of other causes. Epilepsies in DS have a trimodal distribution with age-related phenotypes, etiologies, and prognosis. The most common epilepsy syndrome in infancy is the often-self-limiting West syndrome; if Lennox–Gastaut syndrome occurs in the later course of development, the seizure prognosis worsens significantly. From the fourth decade of life, myoclonic epilepsy often occurs, which in combination with rapidly progressive Alzheimer's dementia is life-limiting within a few years.

Keywords
Mental retardation · Seizures · Dementia · LOMEDS · Therapy

Introduction

Down syndrome (DS) is the most frequent condition leading to intellectual disability. The cause of DS is the numerical aberration of the 21st chromosome, leading to a typical and widely known phenotype and several age-related comorbidities. A relevant diagnostic and therapeutic challenge in people with DS (PWDS) is the increased prevalence of episodic disorders, including epileptic seizures of variable etiologies, falls, fainting, and other seizure mimics.

General demographic data

The prevalence of DS varies considerably from country to country and continent to continent. With increasing maternal age at birth and changes in attitude to abortion and to people with disabilities, the prevalence of DS in the European Union increased from an average of 16 per 10,000 live births in 1990 to 23 in 2015 [16]. In the United States, population-based surveillance programs of birth defects showed that there were 14.85 newborns with DS per 10,000 live births between 2004 and 2010 [27]. Up to the age of 40, mortality in patients with DS hardly differs from other patients with intellectual disabilities but it increases after that [15]. Since the 1940s, the average life expectancy of PWDS gradually increased from 12 years [31] to around 60 [20]. In our cohort, the median age at death of 42 PWDS was 58 years (see **Fig. 1**). A relevant gender difference in age-dependent mortality among PWDS is still under discussion due to inconsistent study results [12]. There is evidence of higher mortality in standard trisomy 21 or Robertsonian translocations compared with mosaic trisomy 21 [47].

Pathophysiology

The cause of DS is trisomy of all or at least a critical portion of chromosome 21 (47 + 21). In about 95% of cases, DS follows a free (standard) trisomy 21, which means an additional chromosome 21 in all cells [3]. Approximately 3–5% of DS arises from a mosaic trisomy. Here two cell lineages exist, one with the diploid chromosome set and another one with an extra chromosome 21 [46]. Robertsonian translocations are found in about 4% of PWDS. Here, the long arm of chromosome 21 is attached to another chromosome (predominately

Supplementary Information

The online version of this article (https://doi.org/10.1007/s10309-022-00506-8) contains an additional table with frequent associated disorders and diseases in Down syndrome and recommendations for assessment and management.

Supplementary material online – scan QR code

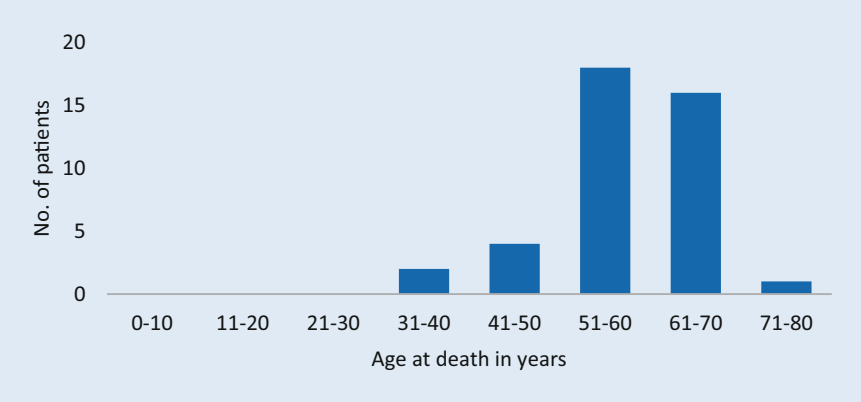

Fig. 1 ▲ Age-related mortality in 42 patients with Down syndrome (data from the Rotenburg Working Group)

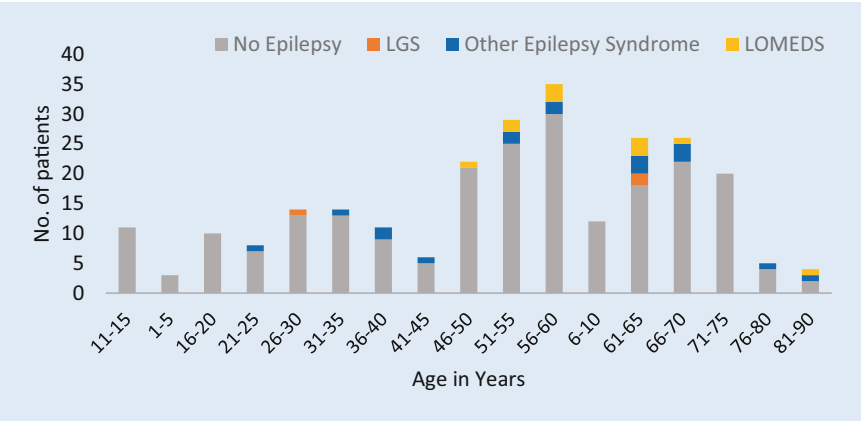

Fig. 2 ▲ Prevalence of epilepsy in 256 people with Down syndrome according to various age groups: The age-independent prevalence of epilepsy was 12.1% ($n = 31/256$; data from the Rotenburg Working Group). *LGS* Lennox–Gastaut syndrome, *LOMEDS* late-onset epilepsy in Down syndrome

chromosome 14), mainly following an error or misdivision after fertilization [5, 29].

Clinical features and comorbidities

People with trisomy 21 show a typical spectrum of physical stigmata, which enables this chromosomal disorder to be easily recognized postnatally (◘ **Table 1**).

People with DS regularly suffer from many concomitant conditions and disorders in different organ systems. Due to the frequent occurrence of behavioral disorders related to cognitive deficits, the risk of undetected or misinterpreted somatic diseases is high. This *diagnostic overshadowing* is a lifelong challenge for PWDS, the attending doctors, and the care environment.

The most frequent associated disorders and diseases in DS and recommendations for assessment and management are listed in the Supplementary Information (Additional Table 1).

Early and late-onset mental impairment

Mental impairment varies from a mild learning disability to severe intellectual disability. Data from industrialized countries revealed an average intelligence quotient (IQ) of children with DS at around 50 (range: 30–70). In the first 3 years of life, the speed of cognitive development is about half that of children without DS. In the following years, the pace of development decreases to around one third. By age 10, children with DS show a developmental age of 4 years [40], eventually reaching a developmental level of 5 years at age 14 [10]. The relatively faster pace of development in the early years but then slowing down seems to be characteristic of children with DS and is different from intellectual disabilities of other causes, including autism [40].

With increasing life expectancy, elderly PWDS have a significantly higher incidence of Alzheimer's dementia (AD) compared with the general population [7]. In DS, AD is often accompanied by myoclonic epilepsy. Clinical symptoms of AD appear in more than half of PWDS over the age of 60 [13]. Most studies report the onset of dementia to be between 50 and 55 years (range: 38–70; [25, 34]). Often, AD in DS follows a rapid progression with an average survival time after dementia onset of 3–5 years [13]. Behavioral disorders are one of the leading clinical indicators for AD in DS, especially in the early stages [11]. In PWDS with pre-existing severe intellectual disability, it may be difficult to distinguish between the latter and symptoms of AD, not least because the transition is usually fluid in terms of time and symptoms. In the course of AD in PWDS, there is a rapidly increasing motor impairment, leading to immobilization and the need for extensive comprehensive care within months.

The relatively high prevalence of AD in DS is presumably caused by the increased probability of triplication and overexpression of the gene coding amyloid precursor protein (APP) on chromosome 21q21.3 [11]. Postmortem, histologic findings revealed neurobiological markers of AD, including neurofibrillary tangles, neuritic plaques, and neuron cell loss in almost all PWDS studied [13].

Epilepsy in Down syndrome

Compared with the overall cohort of people with ID, the prevalence of epilepsy in DS is lower. Due to differences in study populations, observation periods, and other methodological issues, data on epilepsy prevalence rates in DS vary considerably, ranging from 0 to 15.7% [33]. The prevalence of epilepsy in 256 PWDS from our group was 12.1% ($n = 31/256$).

Since the clinical features, treatment strategies, and prognosis vary between the different age-related epilepsy syndromes, prevalence should be considered separately for each age group (see ◘ **Figs. 2 and 3**). The age-related epilepsy syndromes in DS are presumably based on

Table 1 Diagnosis of Down syndrome in newborns using the scoring system of Fried [18][a]

Signs of Down syndrome in newborns [18]	Additional signs [37]
– Abundant neck skin – Mouth corners turned downward – Muscular hypotonia – Flat face (incl. flat nasal bridge) – Dysplastic ear – Epicanthal eye folds – Gap between first and second toes – Protruding tongue	– Brachycephaly – Brachydactyly – Broad hands – Duodenal atresia (abdominal swelling, vomiting, missing bowel movements) – 5th finger clinodactyly – Lax ligaments* – Mental retardation* – Open mouth – Short stature

[a]A score of 6 to 8 (showing 6, 7, or 8 of the signs in the left column) is considered clinically proven Down syndrome (DS). The diagnosis is rejected in infants with 0 to 2 signs [18]. The right column of the table lists further typical stigmata for people with DS, with some of them (*Asterisk*) only becoming evident in later stages of development [37]

different etiological processes. Late-onset epilepsy is usually linked to neurodegenerative processes of AD. By contrast, early-onset epilepsies seem to be associated with other epileptogenic abnormalities that have not been definitively elucidated causally. Histological findings revealed lower neuronal density and abnormal neuronal distribution, particularly in cortical layers 2 and 4 [13].

Types and onset of epilepsy in DS

In general, epilepsy in DS has a trimodal distribution with age-dependent phenotypes, etiologies, and prognosis [35]:

West syndrome is the most common encephalopathic epilepsy in children with DS. Infantile spams occur in 5–15% of cases [22]. The age of onset ranges between 4 and 18 months [4]. The etiology is either non-structural and probably related to genetically caused neuronal dysfunction or attributed to secondary hypoxic encephalopathy following congenital heart disease or perinatal hypoxia–ischemia [42]. Other supposed mechanisms for epileptogenesis of early childhood epilepsies in DS are cortical dysgenesis, reduced density of cortical neurons and interneurons with a GABAergic inhibition, changes in the function of ion channels (especially the GluR5 receptor encoded on chromosome 21), and other metabolic disorders in DS [2]. The prognosis of West syndrome in DS is generally good, and long-term seizure control until early infancy is reported in up to 90% of cases [22]. Early and effective treatment of infantile spams in children with DS may improve the neurodevelopmental outcome [14, 22, 44]. Furthermore, there is some evidence of an onset of infantile spasms after infancy being associated with a more favorable neurodevelopmental outcome [22].

Childhood and early adulthood epilepsy

Lennox–Gastaut syndrome (LGS) is the second crucial encephalopathic epilepsy in DS with a mean onset age of 9.1 years (range: 5–16) and about two thirds of cases beginning after the age of 8 [17]. In contrast to West syndrome, seizure prognosis in LGS is much more unfavorable, and seizures often persist for life.

Late-onset myoclonic epilepsy in Down syndrome (LOMEDS)

Since the 1970s, a growing number of publications described the phenomenon of progressive myoclonic jerks associated with dementia in late-stage DS [1, 9, 11, 13, 26]. Due to a uniform seizure semiology, course, and prognosis, the condition was finally recognized as a separate epileptic entity, abbreviated as LOMEDS [30]. Due to the life-limiting course of LOMEDS, comparability with progressive myoclonus epilepsy is postulated [11].

The mean age at LOMEDS onset is between 45.1 [1, 11, 13] and 59 years (own data; see **Fig. 3**). The development of dementia often precedes the seizures [2] and vice versa [26]. The average elapsed time between dementia and epilepsy was 6.9 months [11]. Based on the data from 12 patients with LOMEDS, three stages of the disease were described [11]:

- Stage 1 (mean age 51 ± 6.6 years): Dementia onset diffuse, electroencephalographic (EEG) changes during sleep, cerebral atrophy on computed tomography (CT)/magnetic resonance imaging (MRI).
- Stage 2 (mean age 51.4 ± 7.2 years): Onset of myoclonus (temporally associated with diffuse epileptiform changes in the waking phase), which antiepileptic drugs can often control.
- Stage 3 (mean age 54.8 ± 7.6 years): Epileptic myoclonus is replaced by non-epileptic myoclonus, cerebellar symptoms, severe dementia, and EEG photosensitivity.

Most patients with LOMEDS develop generalized tonic–clonic seizures as their disease progresses. The first occurrence of the latter often leads to the diagnosis. However, a careful history-taking retrospectively typically reveals pre-existing myoclonus, which is often not sufficiently recognized by the care environment by the time of the epilepsy diagnosis.

Other epilepsy syndromes. Beyond these three main age-dependent categories, epileptic seizures for various reasons (e.g., stroke, traumatic brain injury, tumors, etc.) may occur at any age and do not differ from those in people without DS with or without intellectual disability.

Some authors reported a frequent occurrence of reflex seizures [38]. As with other encephalopathic epilepsies, long-lasting seizure clusters may evolve into refractory non-convulsive status epilepticus. Due to the frequent occurrence of concomitant cardiopulmonary diseases, the risk of sudden unexpected death in epilepsy patients with DS is assumed to be high [39].

EEG findings

In principle, there are no pathognomonic EEG changes for DS. In the absence of seizures or severe neurodegeneration, most PWDS show regular EEG findings, especially in childhood and early adulthood [19]. Early pathological EEG changes are often minor and may present as an alteration of the EEG background activity

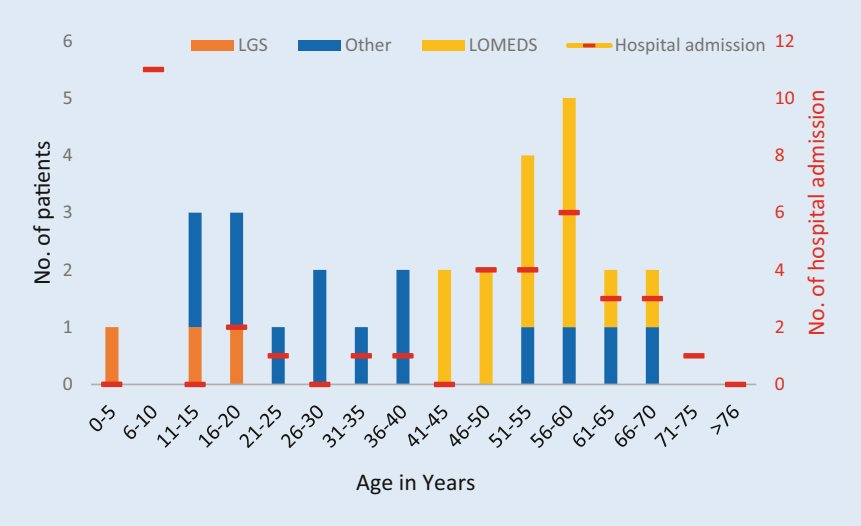

Fig. 3 ▲ Incidence age of epilepsy in 31 people with Down syndrome (*bar chart, left axis of ordinate*) and age at the time of hospital admission for epileptic seizures ($n = 40$; *red crossbars, right axis of ordinate*; data from the Rotenburg Working Group). *LGS* Lennox–Gastaut syndrome, *LOMEDS* late-onset epilepsy in Down syndrome, *Other* epilepsy syndromes other than LGS and LOMEDS

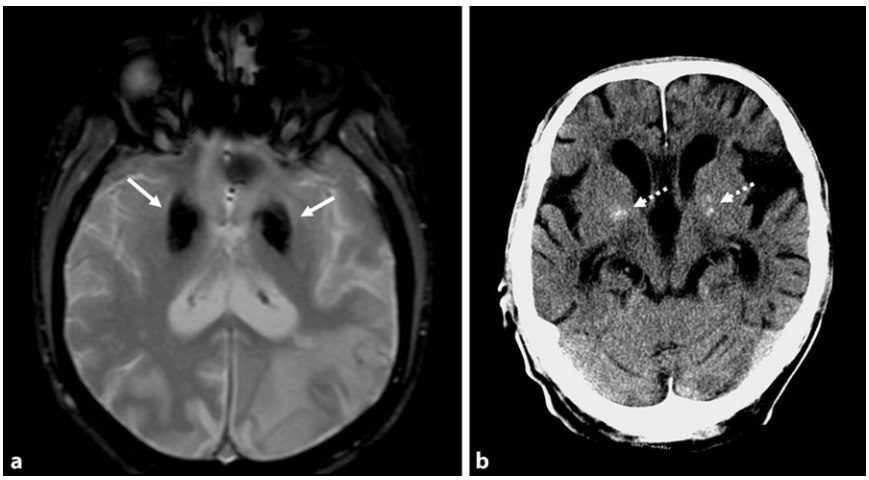

Fig. 4 ▲ **a** Magnetic resonance imaging (MRI) of a 47-year-old patient with Down syndrome and structural focal epilepsy after ischemic infarction in the territory of the left middle cerebral artery. Note the generalized atrophy and the bilateral MRI hypointense signals in the basal ganglia (*white arrows*), indicating calcification. **b** Computed tomography scan of a 65-year-old patient with dementia and epilepsy. The generalized atrophy and hyperdense areas (*dashed white arrows*) indicate bilateral basal ganglia calcification

[36]. Like people without DS, pathological EEG findings depend on epilepsy and its syndromic assignment.

People with DS with infantile spasms show typical interictal hypsarrhythmia with random high-voltage slow waves and spikes arising from multiple foci and spreading to various cortical areas. Seizure patterns present as low-amplitude fast activity [41]. While some authors used EEG-normalization after successful treatment of infantile spasms in PWDS for therapy control, there is no evidence of pretreatment EEG findings being predictive of seizure prognosis [22, 41].

The EEG in LGS typically consists of the triad of (a) slowed background activity, (b) slow spike and wave patterns (mostly bilateral synchronous, repeated at 1–2 Hz), and (c) burst of mostly bilateral low-amplitude fast activity with or without polyspike and wave complexes, the latter predominantly present in slow sleep or as seizure patterns in tonic seizures [8].

In PWDS over 35 years of age, the frequency of generalized EEG slowdowns increases more strongly with progressive dementia [11, 28].

The EEG recordings of 25 adult PWDS from our group showed pathological beta activity (8%), generalized slow theta or delta activity (72%), and focal slow activity (12%). Interictal epileptiform discharges were generalized in 20% of cases and focal in 16% of cases, while ictal seizure patterns were 4.2% generalized and 8.3% focal.

With ongoing dementia in patients with LOMEDS, the physiological EEG background activity is increasingly replaced by generalized theta or delta activity [1], interictal fast spike waves, polyspikes, polyspike and waves, or photoparoxysmal response [9]. Myoclonic seizures are not necessarily associated with ictal epileptiform discharges, especially in the late course of the disease, as an indicator of non-epileptic myoclonus.

CT and MRI findings in DS

The main finding in cerebral CTs and MRIs of PWDS with or without epilepsy is generalized atrophy, more rarely focal or infratentorial [1, 13]. In our series of 28 PWDS, generalized atrophy was found in 25% and post-ischemic lesions in 17.8%. In a series of 21 PWDS with LGS (average age at epilepsy onset: 9.1 years [17]), generalized brain atrophy was found in the majority of these patients too. Therefore, it can be assumed that generalized brain atrophy is not primarily a consequence of secondary neurodegeneration in DS with LOMEDS and AD, but probably represents a superordinate finding in DS.

Another common cerebral finding is basal ganglia calcification in 10.7–26.7% of PWDS ([23]; see ◘ **Fig. 4**). As one study described basal ganglia calcification more frequently in young PWDS [23], a relationship with the premature aging characteristic of DS was postulated [23]. The CT and MRI scans of our 28 adult PWDS showed mild ($n = 10$) or severe ($n = 2$) calcification in the basal ganglia. In contrast to the aforementioned study, we did not see any absolute predominance of basal ganglia calcification in younger patients. Histological and histochemical postmortem studies showed a maximum of calcification in the

Table 2 Recommendations for the diagnosis, treatment, and follow-up of people with Down syndrome and epilepsy

Epilepsy in DS: general recommendations	Specific recommendations in LOMEDS
– Structured anamnesis with patient and caregivers* – Neurological examination* – Note possible triggers (e.g., metabolic disturbances, infections, sleep deprivation, medication failure, traumatic brain injury)* – Home videos and/or video-EEG as soon as possible after episodes or relevant changes in seizure semiology* – Limit long-term antiepileptic medication to a high risk of recurrence, dangerous, and/or distressing seizure semiology, and realistic expectation of significant seizure reduction*, ** – Unless established focal origin of seizures, use broad-spectrum AED* – Monotherapy is preferred* – Monitoring seizure frequency, treatment compliance, tolerance, and possible interactions (drug monitoring if reasonable)*	– Myoclonus not always have an epileptic etiology (e.g., metabolic) → Attention to both underdiagnosis and overdiagnosis* – Use broad-spectrum AED (first choice VPA or LEV)* – Start low, go slow* – When the burden of therapy outweighs the burden of seizures, no treatment is an option** – Avoid sodium channel blockers and GABAergic AED as they may worsen myoclonic jerks* – Epilepsy is not a criterion either for withdrawing or not initiating treatment with anticholinesterase drugs* – Evaluate the coexistence of relevant sleep disturbances (e.g., OSA), which can aggravate seizure control* – Early determination of therapeutic exit strategies** – Early survey of the expressed or presumed patient's will regarding … – … placement of feeding tubes in the case of expected swallowing disorders** – … limitations of intensive care measures**

AED antiepileptic drug, *DS* Down syndrome, *EEG* electroencephalography, *LEV* Levetiracetam, *LOMEDS* late-onset epilepsy in Down syndrome, *OSA* Obstructive Sleep Apnea, *VPA* valproate
*From [2], adapted and added**

pericapillary space and the media of small arteries, whereas the neurons remained unchanged [43].

Treatment of epilepsy in DS

The principles of antiepileptic pharmacotherapy in patients with DS do not differ significantly from those in diploid patients. Scientific studies on the possible superiority of individual antiepileptic drugs in epilepsy in PWDS do not exist. The tolerance of antiepileptic drugs in PWDS may be reduced, especially in the older age, and often only lower doses are well tolerated. Due to the increased prevalence of cardiac malformations in PWDS, antiepileptic drugs with potential arrhythmogenic side effects should be avoided. As in patients without DS, unclassified epilepsies should be treated with broad-spectrum antiepileptic drugs. Because of its potentially pro-myoclonic side effects, lamotrigine should be used with caution in LOMEDS. Data from mostly older studies show frequent use of enzyme-inducing antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, or barbiturates [24], the latter additionally having the problem of a possible negative impact on cognition and behavior. Even if these substances have not entirely lost their place in today's treatment strategies, AED with a more favorable pharmacokinetic profile and fewer side effects should principally be preferred.

When choosing suitable AED, administration aspects (e.g., suspension vs. tablets, tablet size, dosage frequency, etc.) should be considered since a significant proportion of PWDS show a general aversion to taking pills or suffer from significant dysphagia.

Treatment of West syndrome in DS

Infantile spasms are treated in the same way as in other forms of West syndrome, including adrenocorticotropic hormone (ACTH; [2]). As mentioned earlier, despite its higher prevalence in DS, the response to early treatment with ACTH seems to be better than in the general population, with less risk of seizure recurrence in the long term [2]. Besides ACTH, several other AEDs are effective in West syndrome in DS such as vigabatrin, valproate topiramate, and levetiracetam [2].

Treatment of Lennox–Gastaut syndrome in DS

As in LGS of other causes, many AEDs have been used to treat LGS in DS [17]. According to our own experiences and based on various step-by-step LGS treatment regimens [6], valproate in monotherapy or combination with sodium channel blockers (e.g., lamotrigine, lacosamide, or dibenzazepines) is recommended first. In the case of insufficient treatment success, a change or expansion by second-line AED (e.g., levetiracetam, topiramate, clobazam, or felbamate) and/or the use of orphan drugs against LGS (e.g., cannabidiol [45] or rufinamide [21]) is recommended.

As known for LGS in general, administration of benzodiazepines may lead to paradoxical seizure worsening in some patients, possibly requiring immediate antagonization [32]. In such cases, choosing emergency medication with a short half-life (e.g., midazolam) or switching to non-benzodiazepines (e.g., off-label use of chloral hydrate) may be beneficial.

Treatment of LOMEDS in DS

Most authors recommend a treatment of myoclonic jerks in LOMEDS with valproate (500–1000 mg/day [1, 13]) and levetiracetam (500–2000 mg/day [1, 13]). Rarely topiramate (100 mg/day [13, 30]), lamotrigine (50 mg/day [1, 13]), carbamazepine [1], and clonazepam [1] are used. In our experience, even low doses of AEDs are poorly tolerated in the late stages of LOMEDS. Consequently, a careful balancing of treatment goals is strongly recommended. In late-stage LOMEDS, daily doses of valproate and/or levetiracetam of 500 mg each or less may be a reasonable compromise between tolerability and efficacy. At this final stage, the primary goal of therapy may change solely to suppress GTCS while accepting the continuous myoclonic jerks in the meantime.

Summary

Due to different epilepsy syndromes, the high number of possible comorbidities, and an early onset of neurodegeneration, the diagnosis and treatment of epilepsy and other seizure disorders pose a challenge in the care of people with Down syndrome; this requires a transparent, coordinated, and interdisciplinary care setting. A summary of general and specific recommendations for diagnosing, treating, and following up people with Down syndrome and epilepsy is listed in **Table 2**.

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Declarations

Conflict of interest. F. Bösebeck declares that he has no competing interests.

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, and thus supporting data are not available.

Zusammenfassung

Epilepsie und andere Komorbiditäten beim Down-Syndrom

Das Down-Syndrom (DS) ist die häufigste Ursache für Intelligenzminderung. Aufgrund vieler genetischer und – in der Folge – biochemischer Aberrationen findet sich beim DS eine große Anzahl somatischer Störungen und Begleiterkrankungen. Epilepsien treten häufiger auf als in der Normalbevölkerung, jedoch seltener als bei Intelligenzminderung anderer Ursache. Epilepsien bei DS haben eine trimodale Verteilung mit altersabhängigen Phänotypen, Ätiologien und Prognosen. Das häufigste Epilepsiesyndrom im Kleinkindalter ist das oft selbstlimitierende West-Syndrom. Kommt es im späteren Entwicklungsverlauf zu einem Lennox-Gastaut-Syndrom, verschlechtert sich die Anfallsprognose relevant. Ab der 4. Lebensdekade kommt es häufig zu einer Myoklonusepilepsie, welche in Verbindung mit einer rasch progredienten Alzheimer-Demenz innerhalb von wenigen Jahren lebensbegrenzend ist.

Schlüsselwörter
Geistige Behinderung · Epileptische Anfälle · Demenz · LOMEDS · Therapie

References

1. Aller-Alvarez JS, Menendez-Gonzalez M et al (2017) Myoclonic epilepsy in Down syndrome and Alzheimer disease. Neurologia 32:69–73
2. Altuna M, Gimenez S, Fortea J (2021) Epilepsy in Down syndrome: a highly prevalent comorbidity. J Clin Med 10(13):2776. https://doi.org/10.3390/jcm10132776
3. Antonarakis SE (1993) Human chromosome 21: genome mapping and exploration, circa 1993. Trends Genet 9:142–148
4. Arya R, Kabra M, Gulati S (2011) Epilepsy in children with Down syndrome. Epileptic Disord 13:1–7
5. Asim A, Kumar A et al (2015) Down syndrome: an insight of the disease. J Biomed Sci 22:41
6. Bast T (2021) Lennox-Gastaut-Syndrom: Wie behandeln? Z Epileptol 34:136–145
7. Bittles AH, Bower C et al (2007) The four ages of Down syndrome. Eur J Public Health 17:221–225
8. Blume WT, David RB, Gomez MR (1973) Generalized sharp and slow wave complexes. Associated clinical features and long-term follow-up. Brain 96:289–306
9. Crespel A, Gonzalez V et al (2007) Senile myoclonic epilepsy of Genton: two cases in Down syndrome with dementia and late onset epilepsy. Epilepsy Res 77:165–168
10. Crombie M, Gunn P (1998) Early intervention, families, and adolescents with Down syndrome. Intl J Disabil Dev Educ 45:253–281
11. d'Orsi G, Specchio LM, Apulian Study Group on Senile Myoclonic Epilepsy (2014) Progressive myoclonus epilepsy in Down syndrome patients with dementia. J Neurol 261:1584–1597
12. Day SM, Strauss DJ et al (2005) Mortality and causes of death in persons with Down syndrome in California. Dev Med Child Neurol 47:171–176
13. De Simone R, Puig XS et al (2010) Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. Seizure 19:383–389
14. Eisermann MM, Delaraillère A et al (2003) Infantile spasms in Down syndrome—effects of delayed anticonvulsive treatment. Epilepsy Res 55:21–27
15. Esbensen AJ (2010) Health conditions associated with aging and end of life of adults with Down syndrome. Int Rev Res Ment Retard 39:107–126
16. Eu-Science-Hub (2019) Down syndrome in Europe—has the disorder epidemiology changed over the last quarter-century?
17. Ferlazzo E, Adjien CK et al (2009) Lennox-Gastaut syndrome with late-onset and prominent reflex seizures in trisomy 21 patients. Epilepsia 50:1587–1595
18. Fried K (1980) A score based on eight signs in the diagnosis of Down syndrome in the newborn. J Ment Defic Res 24:181–185
19. Gibbs EL, Gibbs FA, Hirsch W (1964) Rarity of 14- and 6-per-second positive spiking among mongoloids. Neurology 14:581–583
20. Glasson EJ, Sullivan SG et al (2002) The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clin Genet 62:390–393
21. Glauser T, Kluger G et al (2008) Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology 70:1950–1958
22. Goldberg-Stern H, Strawsburg RH et al (2001) Seizure frequency and characteristics in children with Down syndrome. Brain Dev 23:375–378
23. Ieshima A, Kisa T et al (1984) A morphometric CT study of Down's syndrome showing small posterior fossa and calcification of basal ganglia. Neuroradiology 26:493–498
24. Johannsen P, Christensen JE et al (1996) Epilepsy in Down syndrome—prevalence in three age groups. Seizure 5:121–125
25. Lai F, Williams RS (1989) A prospective study of Alzheimer disease in Down syndrome. Arch Neurol 46:849–853
26. Li LM, O'Donoghue MF, Sander JW (1995) Myoclonic epilepsy of late onset in trisomy 21. Arq Neuropsiquiatr 53:792–794
27. Mai CT, Isenburg JL et al (2019) National population-based estimates for major birth defects, 2010–2014. Birth Defects Res 111:1420–1435
28. Mcvicker RW, Shanks OE, Mcclelland RJ (1994) Prevalence and associated features of epilepsy in adults with Down's syndrome. Br J Psychiatry 164:528–532

29. Mikkelsen M (1977) Down syndrome: cytogenetical epidemiology. Hereditas 86:45–50
30. Moller JC, Hamer HM et al (2001) Late-onset myoclonic epilepsy in Down's syndrome (LOMEDS). Seizure 10:303–306
31. Penrose LS (1949) The incidence of mongolism in the general population. J Ment Sci 95:685–688
32. Perucca E, Gram L et al (1998) Antiepileptic drugs as a cause of worsening seizures. Epilepsia 39:5–17
33. Prasher VP (1995) Epilepsy and associated effects on adaptive behaviour in adults with Down syndrome. Seizure 4:53–56
34. Prasher VP, Krishnan VHR (1993) Age of onset and duration of dementia in people with Down syndrome: Integration of 98 reported cases in the literature. Int J Geriat Psychiatry 8:915–922
35. Pueschel SM, Louis S, Mcknight P (1991) Seizure disorders in Down syndrome. Arch Neurol 48:318–320
36. Rahman MM, Fatema K (2019) Seizures in down syndrome: an update. Mymensingh Med J 28:712–715
37. Roizen N (2002) Down syndrome. In: Batshaw M (ed) Children with disabilities. Brookes, Baltimore, pp 307–320
38. Romano C, Tine A et al (1990) Seizures in patients with trisomy 21. Am J Med Genet Suppl 7:298–300
39. Scorza CA, Scorza FA et al (2011) Sudden unexpected death in people with Down syndrome and epilepsy: another piece in this complicated puzzle. Clinics (Sao Paulo) 66:719–720
40. Sigman M, Ruskin E et al (1999) Continuity and change in the social competence of children with autism, Down syndrome, and developmental delays. Monogr Soc Res Child Dev 64:1–114
41. Silva ML, Cieuta C et al (1996) Early clinical and EEG features of infantile spasms in Down syndrome. Epilepsia 37:977–982
42. Stafstrom CE, Konkol RJ (1994) Infantile spasms in children with Down syndrome. Dev Med Child Neurol 36:576–585
43. Takashima S, Becker LE (1985) Basal ganglia calcification in Down's syndrome. J Neurol Neurosurg Psychiatry 48:61–64
44. Tapp S, Anderson T, Visootsak J (2015) Neurodevelopmental outcomes in children with Down syndrome and infantile spasms. J Pediatr Neurol 13:74–77
45. Thiele E, Marsh E et al (2019) Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia 60:419–428
46. Thuline H, Puesche S (1982) Cytogenetics in Down syndrome. In: Pueschel S, Rynders J (eds) Advances in biomedicine and the behavioral sciences. Ware Press, Cambridge, p 133
47. Zhu JL, Hasle H et al (2013) Survival among people with Down syndrome: a nationwide population-based study in Denmark. Genet Med 15:64–69