Psychosocial Aspects of Dravet Syndrome

A Population Based Study

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To Helena, the love of my life

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ABSTRACT

Dravet syndrome (DS) is a developmental and epileptic encephalopathy, associated with significant neurodevelopmental comorbidity. The aims of this population-based study were to describe the epidemiology, genetics, mortality, seizure burden, and treatments in Swedish children with DS (Paper I), to describe seizure-provoking factors and strategies to avoid seizures (Paper II), cognitive function and adaptive behaviour (Paper III), and behaviour, sleep-problems and quality of life (Paper IV).

We identified 55 children born 2000–2018. A semi-structured interview regarding seizure burden, treatments, seizure-provoking factors, and strategies to avoid seizures was used (Papers I and II). The Vineland Adaptive Behaviour scales and Wechsler or Griffiths scales were used to assess adaptive behaviour and intellectual function (Paper III). In paper IV we used the Developmental Behaviour Checklist, the Insomnia Severity Index and a global question regarding the child´s quality of life.

Of 53 children, 51 (96%) had a variant in the *SCN1A*-gene. Seven (13%) had died. When comparing `younger´ children (born 2010-2018) with `older´ (born 2000-2009), median age at diagnosis was lower, the use of contra-indicated sodium channel inhibitors was lower, and the cumulative incidence was higher in `younger ´children. Status epilepticus was seen in 90%, tonic seizures in 60%, focal to bilateral tonic clonic seizures in 98% and myoclonic seizures in

83% (Paper I). Seizure precipitants and strategies to prevent seizures were reported in all children. Most common were febrile and afebrile infections (100%, 93%). Most avoided were warm weather (83%) and physical activity (64%) (Paper II). Intellectual Disability was seen in 86% of the children and 93% had difficulties with adaptive behaviour (Paper III). Problems with behaviour was seen in 72%, `moderate´ or `severe´ insomnia in 43%, and `poor´ or ´very poor´ quality of life in 17% of children (Paper IV).

This is one of the first population-based studies that describes psychosocial aspects of DS. We confirm the high mortality and high seizure burden. Results suggest increased knowledge in Sweden leading to earlier diagnosis and improved treatment. The high number of reported seizure provoking factors and measures taken to avoid seizures, the high proportion of ID, behavioural and sleep problems can significantly affect the child and the whole family.

Keywords: Anticonvulsants, behaviour, children, Dravet syndrome, demography, intellectual disability, mortality, prevention, precipitants, quality of life, sleep.

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SAMMANFATTNING PÅ SVENSKA

Syftet med denna avhandling är att identifiera alla svenska barn, med diagnosen Dravets syndrom (DS), födda 2000–2018 och att genomföra en befolkningsbaserad studie med fokus på psykosociala aspekter.

DS är ett sällsynt och svårbehandlat epilepsisyndrom med flera olika anfallstyper och hög frekvens av långvariga epilepsianfall, status epilepticus. Sjukdomen debuterar vanligtvis under det första levnadsåret. Anfallen består initialt av ryckningar i ena eller båda sidorna av kroppen, men efter hand får barnen andra typer av epilepsianfall. Det är vanligare än vid andra typer av epilepsisyndrom att epilepsianfallen utlöses av infektioner med och utan feber, lätt förhöjd kroppstemperatur, på grund av fysisk aktivitet eller varm omgivning och även av starka känslor som till exempel glädje. Epilepsirelaterad död är också vanligare, framför allt under de första tio levnadsåren.

Under de första fem levnadsåren stagnerar utvecklingen och mer än 80% av barnen utvecklar intellektuell funktionsnedsättning (IF). Problem med beteende och sömn är vanligt, liksom problem med uppmärksamhet och sociala kontakter. Även motoriska symptom med ökad tonus (spasticitet) i benen och svårigheter att samordna rörelser (ataxi och tremor) förekommer.

DS beskrevs första gången 1978 i Frankrike av barnneurologen Charlotte Dravet. Efter hand har kunskapen om sjukdomen ökat och idag beräknar man att två till sex barn av 100 000 drabbas av DS. Forskningen har visat att sjukdomen vanligtvis orsakas av mutationer i *SCN1A*-genen, som kodar för byggstenar i natriumkanalen. Mutationer i genen leder till ökad retbarhet i hjärnan på grund av att natriumkanalen inte fungerar. Dåligt fungerande natriumkanaler kan förklara de flesta symptomen vid sjukdomen, inte bara epilepsin. Utveckling av läkemedel mot epilepsianfall med mer specifik effekt på den skadade natriumkanalen pågår. Idag vet man också att natriumkanalblockerare (en vanlig typ av läkemedel mot epilepsianfall) ska undvikas, då de ytterligare kan försämra funktionen i de drabbade natriumkanalerna.

Det saknas befolkningsbaserad kartläggning av beteendeproblem, sömn och kognitiv funktion och inte minst hur detta svårbehandlade epilepsisyndrom påverkar barnets och vårdnadshavares livskvalitet. För att få en så rättvisande bild som möjligt är det viktigt att man använder frågeformulär och undersökningsinstrument som är anpassade till barn med IF och svårbehandlad epilepsi.

För att hitta alla barn med en DS-diagnos i Sverige använde vi ett register från en tidigare studie. Vi kontaktade epilepsisjuksköterskor och alla svenska barnneurologer. Samtliga medlemmar i den svenska stödföreningen för DS, Dravet Syndrome Association Sweden, informerades om studien via föreningens styrelse. När det gäller bedömning av beteende har vi använt ett frågeformulär som är anpassat till barn med olika grader av IF.

Vi använde följande inklusionskriterier: a) Normal psykomotorisk utveckling och normalt EEG före anfallsstart; b) Första epileptiska anfallet innan ett års ålder; c) Behandlingsresistenta kloniska (anfall med ryckningar) eller tonisk-kloniska anfall (anfall med stelhet som följs av ryckningar). d) Inga påvisbara skador eller missbildningar i hjärnan vid symptomdebut; e) Andra epilepsisyndrom är exkluderade.

Avhandlingen består av fyra delarbeten. De två första bygger på intervjuer med vårdnadshavare. Det tredje bygger på en psykologutredning av barnen. Det fjärde delarbetet består av tre frågeformulär som har fyllts i av vårdnadshavare för att undersöka beteende, sömn och livskvalitet.

Delarbete I: Vi identifierade 55 barn med DS födda mellan 2000 och 2018. Hos 51 av 53 (96%) barn fanns en genetisk variant i SCN1A genen. Sju barn (13%) hade avlidit vid en medianålder på 4,7 år. Vi identifierade således 48 barn med DS vilket innebär att ett av 45 000 barn i Sverige har diagnosen DS. Medianåldern när man upptäckte DS var lägre hos yngre barn, födda 2010–2018 (1,6 år), jämfört med äldre barn, födda 2000–2009 (4,5 år). Andelen barn som hade använt kontraindicerade natriumkanalhämmare som epilepsibehandling var lägre hos yngre barn. Dessa fynd kan tala för att kunskapen om DS och dess behandling har förbättrats.

Delarbete II: I detta delarbete genomförde vi standardiserade intervjuer med vårdnadshavare till 42 barn avseende anfallsprovocerande faktorer och

anfallsförebyggande metoder. Det visade sig att alla vårdnadshavare beskrev anfallsutlösande faktorer och alla angav att de använt strategier för att undvika epilepsianfall. Faktorer som hade utlöst anfall hos minst hälften av barnen var infektioner med och utan feber, fysisk aktivitet, trötthet, varmt väder, starka känslor, sömn och många människor runt barnet. För att undvika epilepsianfall använde minst hälften av vårdnadshavarna en eller flera av följande strategier; undvika att utsätta barnet för varmt väder, att begränsa fysisk aktivitet eller att undvika infektioner, trötthet och många människor i omgivningen. Vid smittsamma infektioner hade två tredjedelar av alla barn hållits hemma från skola/förskola för att undvika infektion och därmed försämring av epilepsin. I familjer med syskon hade syskon i knappt hälften av familjerna hållits hemma från skola/förskola av samma anledning.

Delarbete III: I detta delarbete genomförde vi en psykologisk undersökning av 42 barn och 36 (86%) uppfyllde kriterier för IF. Vid undersökning av adaptiva färdigheter (hur barnet självständig klarar kommunikation, vardagliga färdigheter, sociala färdigheter och motorik jämfört med jämnåriga) fann vi att 39 (93%) hade betydande svårigheter och vi såg att dessa svårigheter ökade med stigande ålder och autistiska symptom.

Delarbete IV: I detta delarbete använde vi frågeformulär för att undersöka problem med beteende och sömn och kartlägga livskvalitet. Dessa formulär fylldes i av vårdnadshavare till 42 barn. Våra resultat visade att vårdnadshavare rapporterade beteendeproblem hos 72%, moderata eller allvarliga sömnproblem hos 43% och dålig eller mycket dålig livskvalitet hos 17%. Ju mer autistiska symptom ett barn hade desto större beteendeproblem hade barnet. Ju större sömnproblem ett barn hade desto sämre var livskvaliteten och desto mer biverkan hade barnet av epilepsimediciner.

Sammanfattning: Detta är en av de första befolkningsbaserade studier av DS i Sverige. Vi beskriver att yngre barn hade fått en DS-diagnos tidigare och behandlats med färre kontraindicerade epilepsimediciner. Majoriteten av barnen hade intellektuell funktionsnedsättning och många barn hade problem med beteende och sömn. Anfallsutlösande faktorer fanns hos alla barn och hos alla användes strategier för att undvika anfall. Dessa faktorer förefaller påverka livskvaliteten hos barnet och familjen. Vi hoppas att våra resultat ger ökad kunskap om DS och kan förbättra förståelse för och omhändertagandet av DS och bidra till adekvat hjälp från vård, skola och socialtjänst. Vi hoppas

dessutom att våra resultat kan förbättra förståelse för och omhändertagande av barn med andra liknande epilepsisyndrom med kognitiva och beteendemässiga problem.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Bjurulf, B**., Reilly, C., Sigurdsson, G.V., Thunstrom, S., Kolbjer, S., Hallböök, T. Dravet syndrome in children-A population-based study. *Epilepsy Res 2022; 182: 106922*.

II. **Bjurulf, B**., Reilly, C., Hallböök, T. Caregiver reported seizure precipitants and measures to prevent seizures in children with Dravet syndrome. *Seizure 2022; 103: 3-10.*

III. Reilly, C., **Bjurulf, B**., Hallböök, T. Intellectual functioning and adaptive behaviour in children with Dravet syndrome: A population-based study. *Dev Med Child Neurol. 2022; 65(6): 831-837.*

IV. **Bjurulf B**., Reilly, C., Hallböök, T., Caregiver reported Behavior, Sleep and Quality of Life in Children with Dravet Syndrome: A population-based study. Accepted manuscript, *Epilepsy Behav. 2023.*

CONTENTS

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorders
ASM	Anti-Seizure Medication
CBCL	Child Behavior Checklist
CI	Confidence Interval
CRF	Case Report Form
DBC-2	The Developmental Behavior Checklist – Second Edition
DEE	Developmental and Epileptic Encephalopathy
DQ	Developmental Quotient
DS	Dravet Syndrome
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EEG	Electroencephalogram
ELDQOL Scale	Epilepsy and Learning Disability Quality of Life Scale
GABA	Gamma-Aminobuturic Acid
GEFS+	Genetic Epilepsy with Febrile Seizures Plus
GTC	Generalised Tonic-Clonic Seizure
HRQoL	Health-Related Quality of Life
IBM	International Business Machines Corporation

ID	Intellectual Disability
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
ISI	The Insomnia Severity Index
Na_V 1.1	Type I Voltage-Gated Sodium Channel
NREM	Non-Rapid Eye Movement
PDCH19 gene	The gene coding for Protocadherin 19
QoL	Quality of Life
QOLCE-76	Quality of Life Childhood Epilepsy Questionnaire – 76 Questions
REM	Rapid Eye Movement
SCN1A gene	The gene coding for Sodium Voltage-gated Channel Alpha, Subunit
SCQ	Social Communication Questionnaire
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SE	Status Epilepticus
SPSS	Statistical Package for the Social Sciences
SUDEP	Sudden Unexpected Death in Epilepsy
VABS-II	Vineland Adaptive Behavior Scales – Second Edition
WAIS	Wechsler Adult Intelligence Scale

WHO	World Health Organization
WISC-5	Wechsler Intelligence Scale for Children – Fifth Edition
WPPSI-IV	Wechsler Preschool and Primary Scaler of Intelligence – Fourth Edition

THESIS AT A GLANCE

Paper	Aims	Methods	Results	Conclusion
I. Epidem-iology, genetic profile, mortality, seizures, and treatments in Swedish children with DS	To investigate seizures, genetic profile, mortality, epidem-iology, and treatments	We performed a population-based study of children with DS. `Younger´ children born 2010-2018 were compared with `older´ children born 2000-2009	We found 55 children with DS. Seven (13%) had died. CI was higher, median age at DS diagnosis was lower and fewer children had used contra-indicated ASMs in `younger´ children	The knowledge of DS seems to have improved with time. The number of patients with a DS diagnosis had increased, with DS diagnosis at an earlier age. The use of contraindicated ASMs was reduced in `younger´ children
II. Seizure provoking factors	To investigate seizure precipitant s and measures other than ASMs to avoid seizures in DS	We performed in-depth interviews with caregivers of 42/48 (88%) children with DS in Sweden	Seizures had been provoked by fever in all, and by afebrile infections in 39/42 (93%). Warm weather had been avoided by 35/42 (83%) and physical activity by 27/42 (64%)	Seizure-provoking factors were identified in all children with DS. Measures other than ASMs to avoid seizures had been taken in all children with DS
III. Intellectual function	To investigate intellect-ual function and adaptive behaviour in DS	A neuro-psychologist assessed intellectual function and adaptive behaviour in 42 children	DSM-5 criteria for ID were fulfilled in 36/42 (86%) children and 39/42 (93%) had an adaptive behaviour score <2 SD below mean	Most children with DS had ID and significant impairments in adaptive behaviour
IV. Behaviour, sleep, QoL	To investigate behaviour, insomnia, and QoL in DS	Caregivers responded to validated questionnaires in 42 children	Behavioural problems were seen in 29/40 (72%) children, significant insomnia in 18/42 (43%), and poor QoL in 7/41 (17%)	Problems with behaviour and sleep are common in DS, often affecting QoL

ASMs, Anti-Seizure Medications; CI, Confidence interval; DS, Dravet Syndrome; DSM-5, Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; QoL, Quality of Life; SD, Standard Deviations

1 INTRODUCTION

DS is a genetically well-defined Developmental and Epileptic Encephalopathy (DEE)[1], usually caused by pathogenic variants in the *SCN1A* gene[2]. Children with DS have a drug-resistant epilepsy with a high seizure burden[3], and high epilepsy-related mortality[4-6]. Seizures are often reported to be provoked by increased temperature and emotions according to caregivers[7]. Most children develop ID[1]. Behavioural problems[8-10] and sleep-related problems[11-15] are common. All these factors can affect quality of life (QoL) for the child and for the whole family[11, 13]. There are few comprehensive population-based studies of DS.

The aim of this study was is to investigate population-based data on different aspects of DS and thus reduce the risk for selection-bias. We have investigated epidemiology, mortality, genetics, seizure types, epilepsy treatments, and reported seizure provoking factors in DS as well as strategies to avoid seizures, intellectual function, behaviour, sleep, and QoL. We hope that our study will increase awareness of DS and lead to improved care for the children and their families.

1.1 DEFINITION OF DS AND MAIN CHARACTERISTICS

Dravet syndrome (DS) (OMIM 607208) is one of the most well-defined and extensively studied DEEs[16]. It is a channelopathy usually due to a dominant pathogenic variant (i.e., mutation), in the *SCN1A* (sodium channel alpha 1 subunit) gene[2]. This gene encodes the type I voltage-gated sodium channel ($Na_V1.1$) alpha subunit[2]. DS was previously known as Severe Myoclonic Epilepsy of Infancy and was first described in 1978 by Charlotte Dravet[17]. The syndrome is classified as a DEE with cognitive and behavioural comorbidities, where symptoms are caused both by the epilepsy and directly by malfunction of the Na_V 1.1 channel[18]. It is a combined generalised and focal epilepsy type[18].

New diagnostic criteria for DS according to the International League Against Epilepsy (ILAE) were published in 2022[1]. According to these criteria, seizures

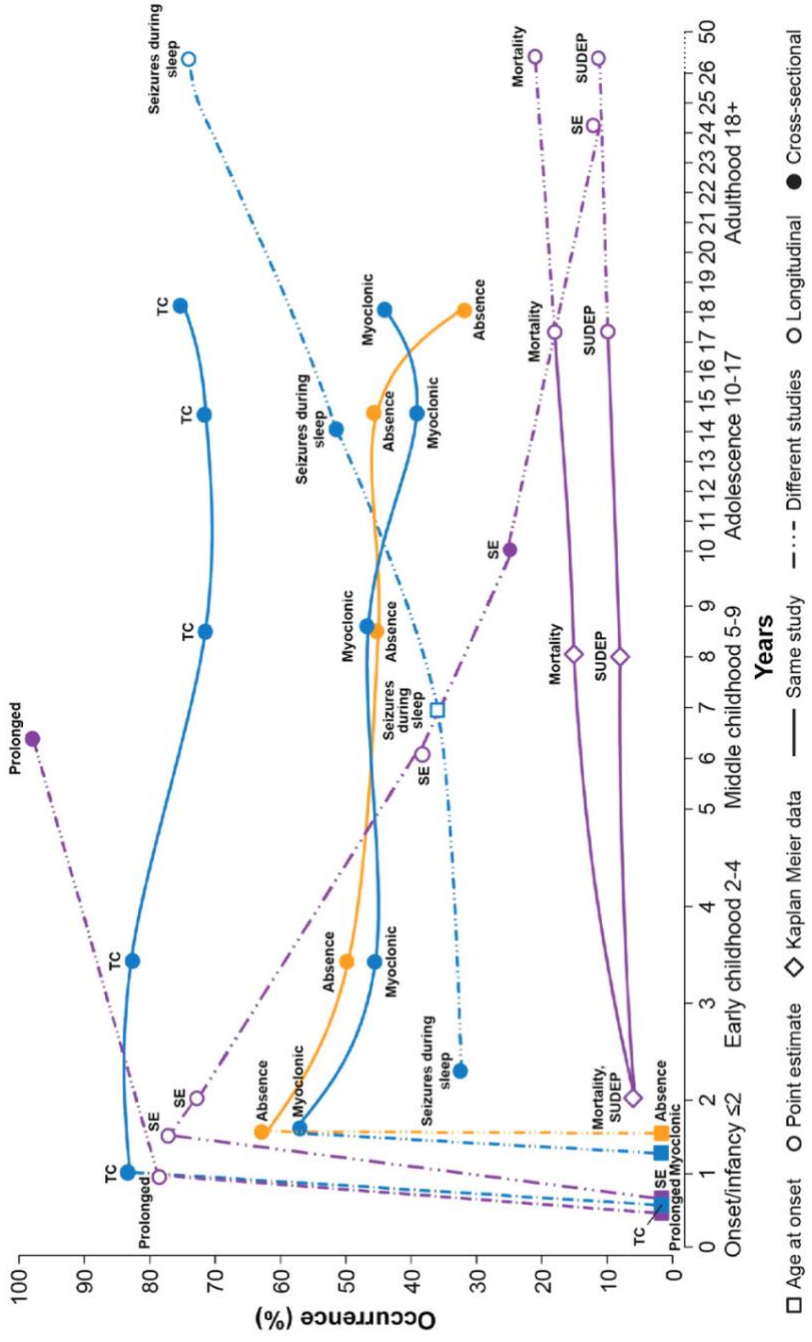
present between the age of 1-20 months in an infant with normal development, head size and neurological examination.

The seizures are recurrent and typically prolonged (>10 minutes) and status epilepticus (SE) is common until adolescence, especially before five years of age. Seizure types include focal clonic, often side-alternating hemiclonic, and/or generalised clonic, and/or focal to bilateral tonic clonic seizures. The children develop drug-resistant epilepsy. Fever, increased external or internal temperature and excitement are some of the factors, that can trigger seizures[1]. Other seizure types can develop between the age of one and four years, but tonic seizures have previously been considered unusual in DS[3]. Development of different seizure types in different ages is presented in Figure 1.

Slowing of the background activity in EEG and interictal discharges are typical after two years of age[1]. Cognitive development slows down or stagnates[19], and most children manifest ID[1]. Gait abnormalities including a characteristic crouch gait, possibly due to muscle weakness and mild spasticity, are manifest from early adolescence[20]. Ataxia and muscular hypotonia are other neuromuscular signs seen in children with DS[3]. Non-seizure related manifestations of DS, according to previous studies, are presented in Figure 2. The syndrome is characterised by a very high rate of epilepsy-related premature death, and the highest rate seems to occur before 10 years of age[4]. Present understanding of mortality in different ages is presented in Figure 1.

Figure 1 (Page 3). Clinical evolution of seizure-related manifestations and mortality in DS: Data from 8 longitudinal studies and 6 large (n>50) cross-sectional studies. Abbreviations: TC, tonic-clonic; SE, status epilepticus; SUDEP, Sudden Unexpected Death in Epilepsy; From Sullivan and co-workers. Epilepsy & Behavior 2022[21]. Open acess. Reproduced with permission.

Figure 2 (Page 4). Clinical evolution of non-seizure-related manifestations in DS: Data from three longitudinal studies and nine large (n>30) cross-sectional studies. From Sullivan and co-workers. Abbreviations: DD, Developmental Delay; ID, Intellectual Disability; ASD, Autism Spectrum Disorders; ADHD, Attention Deficit Hyperactivity Disorder; CG, Crouch Gait. Epilepsy & Behavior 2022[21]. Open acess. Reproduced with permission.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Onset/infancy ≤2
Early childhood 2-4
Middle childhood 5-9
Adolescence 10-17
Adulthood 18+
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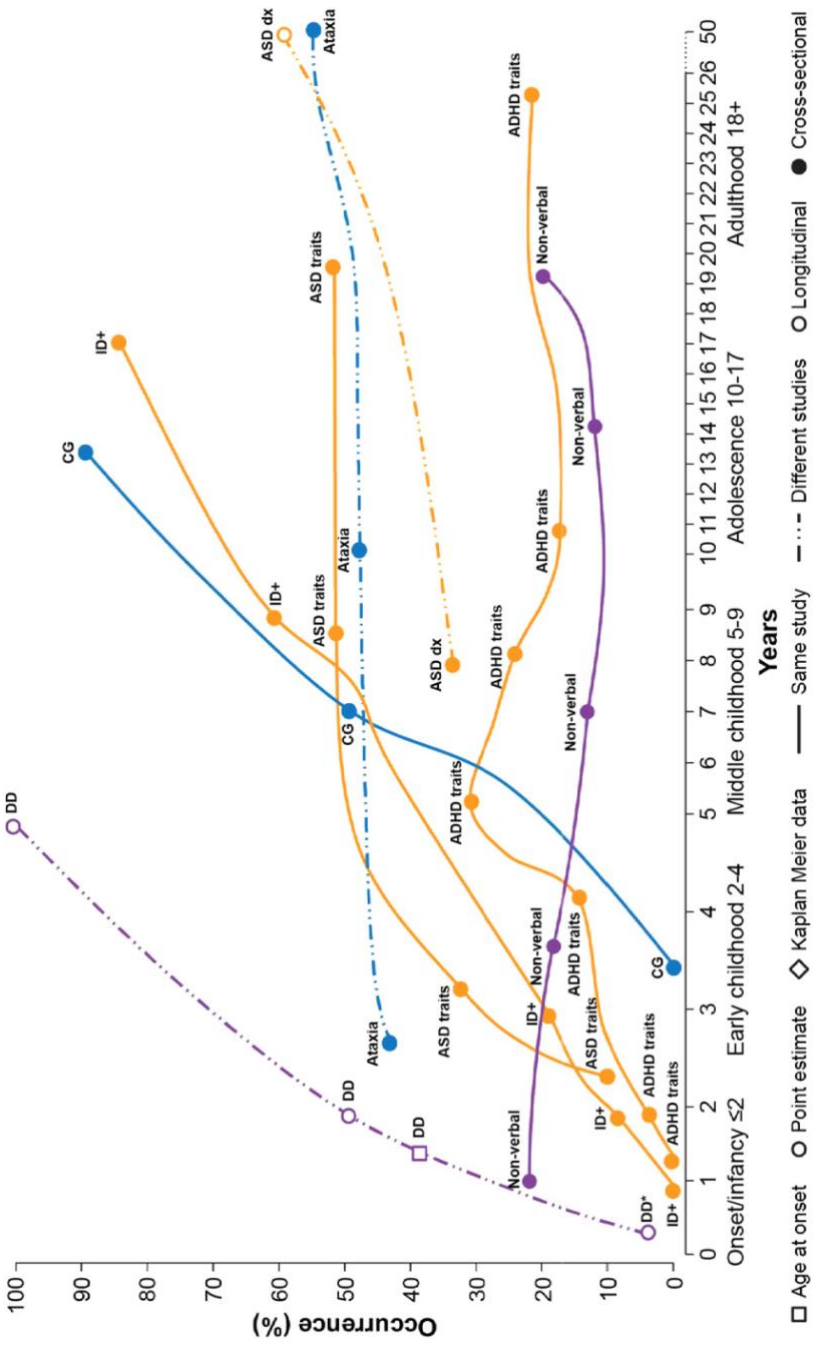
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Point estimate
Kaplan Meier data
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Longitudinal
Cross-sectional
DD
DD*
ID+
CG
Ataxia
ASD traits
ASD dx
ADHD traits
Non-verbal

1.2 THE CONCEPT `DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY´

`Epileptic encephalopathy´ is defined by the ILAE as a condition where the epileptic activity itself contributes to severe cognitive and behavioural impairments above what might be expected from the underlying pathology alone[22]. The abundant epileptiform activity interferes with development resulting in cognitive slowing and often regression, and sometimes is associated with psychiatric and behavioural consequences[22]. Thus, reduction of the epileptiform activity could improve the developmental consequences of the disorder[18].

However, many severe genetic disorders such as DS also have developmental consequences arising directly from the effect of the genetic variant, and it is often impossible to determine which of these contributors is most important[18]. In DS developmental slowing generally occurs between one and two years of age, at a time when epileptiform activity on EEG is usually not yet frequent, indicating a direct effect of the genetic variant[18]. The concept `developmental and epileptic encephalopathy´ (`DEE´) was defined by the ILAE as a condition where the epileptic activity and the underlying genetic variant together cause the encephalopathy[18].

The term `epileptic encephalopathy´ can still be used when there is no pre-existing developmental delay, and when slowing of development is not thought to be caused by a genetic variant[18]. The term `developmental encephalopathy´ can be used when there is developmental impairment without frequent epileptic activity associated with slowing of development[18]. DS is classified as a DEE by the ILAE[1]. Classification of different DEEs is presented in Figure 3.

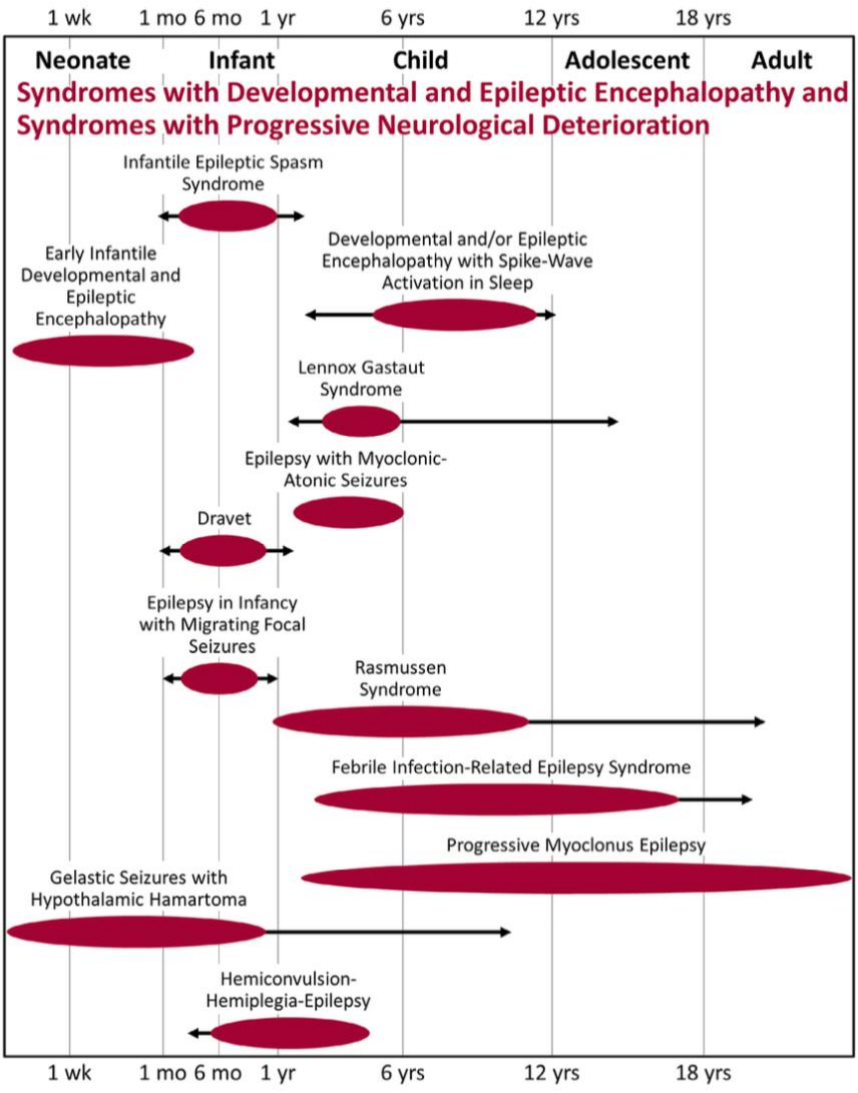

Figure 3. Classification of developmental and epileptic encephalopathies and progressive epilepsy syndromes, based on age at presentation. The typical ages of presentation are shown with ranges indicated by arrows. From Wirrell, E.C et al. Epilepsia 2022[23]. Open access. Reproduced with permission.

1.3 THE *SCN1A*-GENE

DS is an etiologically well-defined epilepsy syndrome, where most cases can be explained by a pathogenic variant in the *SCN1A* gene[1]. The association between this gene and DS was discovered in 2001[2]. The *SCN1A* gene codes for the sodium channel $Na_V1.1$. The structure of this sodium channel is presented in Figure 4.

In most individuals a novel dominant pathogenic *SCN1A* variant is found. However, in some cases of DS, the *SCN1A* variant is inherited from parents, who have a milder phenotype, within the Genetic Epilepsy with Febrile Seizure Plus (GEFS+) spectrum. DS probably represents the extreme end of the GEFS+ spectrum[24]. Low grade parental mosaicism has been detected in the blood of 7-13% of individuals with DS, and the number of mutated cells might be considerably higher in germ cells than in the blood[24-26]. There are also DS cases with recessive inheritance[27].

DS is increasingly perceived as a single gene channelopathy, while pathogenic variants in other single genes are described as separate entities[28]. This might improve precision in diagnosis and prognosis, and facilitate development of new treatments[28]. However, phenotypes due to pathogenic variants of *SCN1A* and of other genes can be clinically indistinguishable, and there are individuals with a typical DS phenotype without a detectable *SCN1A* variant[28].

DS is usually due to loss of function in the *SCN1A* gene[29]. Gain of function in the *SCN1A* gene are associated with familial hemiplegic migraine and with severe neonatal or infantile onset DEEs with movement disorder, and congenital arthrogryposis with neonatal onset[30]. Gain of function in the *SCN1A* gene has also been associated with neonatal onset epilepsy without obvious movement disorder[31]. The GEFS+ spectrum can be correlated to both gain and loss of function in the *SCN1A* gene and with pathogenic variants in other genes and can be sporadic as well as familial[32-34].

The *SCN1A* variants underlying DS do not only cause a severe epilepsy but have also an impact on cognitive development[35, 36], and thus DS is considered a DEE[18, 37]. According to studies on mice, *SCN1A* loss of function variants coding for $Na_V1.1$ channels affect the brain in several ways. In the hippocampus, the $Na_V1.1$ channels are mainly located in inhibitory

GABAergic interneurons, which might explain the neuronal hyperexcitability in individuals with DS[29]. The GABAergic interneurons are critical for regulating the synchrony and temporal patterning of neural networks and thus are believed to have an important role in cognitive development[36]. $Na_V1.1$ channels play a crucial role in the excitability of cerebellar Purkinje neurons, and loss of function in these cells might explain ataxia in individuals with DS[38].

Mice with deleted $Na_V1.1$ channels in the forebrain have impaired function of GABAergic neurons in the reticular nucleus of the thalamus and show a similar type of sleep impairment as DS phenotype mice[39]. An imbalance between excitatory and inhibitory neurons in the thalamocortical network leads to impaired rebound burst firing in this mouse model[39], a firing that is critical for generating EEG slow wave activity and sleep spindles, which drives sleep behaviour[40].

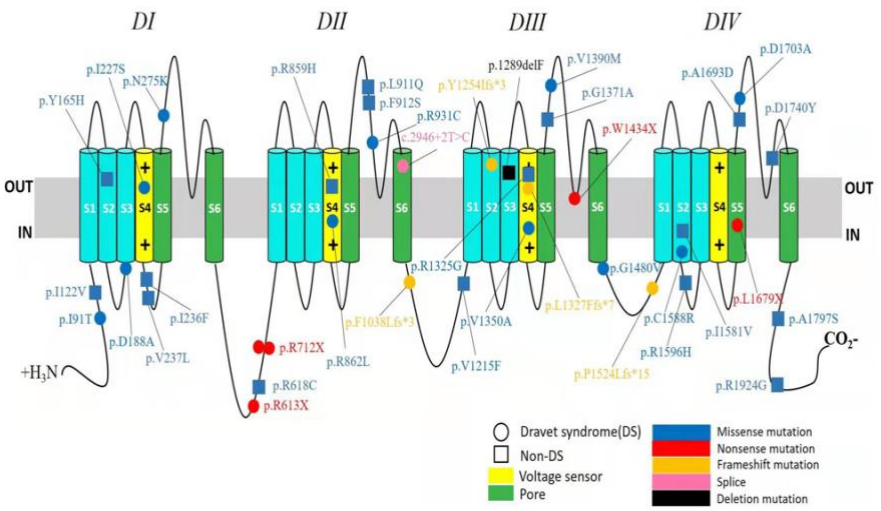

Figure 4. Structure of the human Na_V 1.1 channel. The Na_V 1.1 channel consist of four homologous domains (DI-DIV), each with six transmembrane segments (S1-S6). The fourth segment (S4) of each domain functions as a voltage sensor. The S5 and S6 segments of each domain make up the pore of the channel, and the connecting loop between S5 and S6 is the pore loop. Shown are examples of locations of pathogenic variants in the SCN1A gene leading to Dravet syndrome or less serious phenotypes. From Chen C. et al. Front Mol Neurosci. 2022[41]. Open access. Reproduced with permission.

1.4 MORTALITY

DS is characterized by a very high epilepsy-related premature mortality, probably with the highest rate before 10 years of age[4, 5]. However, there are indications that premature mortality is also high in adults[42, 43]. Current understanding of mortality in different ages is presented in Figure 1.

Sudden unexpected death in epilepsy (SUDEP) is defined as sudden, unexpected death in a person with epilepsy in the absence of a known structural cause, SE or drowning, occurring within one hour after the onset of a known terminal event, whether or not a terminal seizure has occurred[44]. Presence of GTC seizures and the frequency of this seizure type is considered the most important risk factor for SUDEP[45, 46]. According to previous reports, SUDEP accounts for between 50 and 60% of all deaths in DS, SE for 30% and accidents, mainly drowning for 10%[4, 5, 47, 48].

1.5 ANTISEIZURE TREATMENTS

According to international consensus, valproate, clobazam, stiripentol, and fenfluramine may be considered as first or second line anti-seizure medications (ASMs). Cannabidiol is considered a third line ASM[49]. Cannabidiol seems to be associated with a lower rate of seizure-response but with less side-effects compared to stiripentol and fenfluramine, but head-to-head trials are lacking[50]. Ketogenic diet and topiramate are considered fourth line treatments[49]. Cannabidiol and fenfluramine are currently not subsidized in the Swedish public health system.

Sodium-channel blockers such as lamotrigine, phenytoin and carbamazepine usually worsen seizures in DS[51-54], and prolonged use in early life can have negative effects on cognitive outcome[55]. Thus, they are considered contra-indicated according to international guidelines[49].

1.6 SEIZURE PROVOKING FACTORS AND STRATEGIES TO AVOID SEIZURES

Measures to prevent seizures other than ASMs in DS have to our knowledge not been investigated previously, and seizure precipitants have been investigated systematically in only a few studies[7, 56, 57]. A higher number of seizure precipitants, such as infections with and without fever, acute stress, and physical exercise have been reported by caregivers in children with DS, compared to children with an epilepsy diagnosis and seizures within the last two years[7].

Epilepsy severity is correlated to health-related quality of life (HRQoL) in DS[8]. Fewer seizure free days, higher seizure frequency, and a shorter interval without seizures have a negative impact on HRQoL in DS and leads to higher resource utilisation and higher economic costs[58]. A reduction of GTCs in epilepsy in general has been shown to reduce the SUDEP risk, and thus might reduce SUDEP in DS[45]. Seizures in individuals with DS are often drug resistant, and other treatment strategies, including lifestyle adjustments, may be important to control seizures[7]. However, spontaneous worsening of seizures that might start abruptly, has been reported in up to 30% of individuals with refractory epilepsy[59]. Thus, it can be difficult to distinguish seizure worsening due to specific provocative factors from a spontaneously fluctuating epilepsy[60].

There are several factors indicating that seizure precipitants are important in DS. Seizures have been triggered by increasing the body temperature to 38 degrees by immersion in a hot bath in children with DS[56] and by increasing the body core temperature in a DS mouse model[61]. In a cohort with children and adolescents with DS, 99% at least one seizure precipitant was reported[7]. This cohort had more reported seizure provoking factors than a cohort with children with other types of epilepsy. Caregivers' understanding of seizure provoking factors could be affected by recall bias and their explanatory model of epilepsy[62]. However, the high frequency of seizure provoking factors reported by individuals with epilepsy in general and their caregivers, makes it unlikely that the occurrence of precipitants simply is a misconception[62]. A better knowledge of seizure provoking factors might improve the understanding of seizure genesis and support the use of nonpharmacological treatments of seizures[62].

1.7 INTELLECTUAL FUNCTION AND ADAPTIVE BEHAVIOUR

ID is a disorder that includes deficits both in intellectual and adaptive functioning with onset during the developmental period according to the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5)[63].

Three criteria need to be fulfilled for an ID diagnosis according to the DSM-5 manual; Criterion A is met in individuals that have an IQ (intelligence quotient) of approximately two standard deviations or more below the population mean of 100, i.e., 70. Intellectual functioning is measured with psychometrically valid tests of intelligence and involves reasoning, problem solving, planning, abstract thinking, judgement, learning from instruction and experience, and practical understanding.

Criterion B is met when at least one domain of adaptive functioning is sufficiently compromised that ongoing support is needed for the person to perform adequately in at least one life setting such as in school or at home. Adaptive functioning refers to how well an individual meets standard of personal independence and social responsibility, compared with others of similar age and sociocultural background. It involves adaptive competence in three domains: conceptual (e.g., judgement in novel situations, memory, reading, and problem solving), social (e.g., awareness of others´ thoughts, feelings and experiences and social judgement) and practical (i.e., learning, and self-management across life-settings such as personal care and self-management of behaviour).

Criterion C is met when intellectual and adaptive deficits are present during childhood and/or adolescence.

The different levels of ID (mild, moderate, severe, and profound) are, according to DSM-5, defined based on adaptive functioning and not on IQ scores, since it is the adaptive level that determine the level of support needed[63]. Different classification systems for the different levels of ID are described in Table 1. Even though different levels of ID are defined mainly based on adaptive functioning, adaptive functioning has not been evaluated in most studies describing intellectual functioning in DS[9]. Almost all children

with DS develop ID and more than 60% have moderate, severe or profound ID according to previous studies[9].

Table 1 (Page13). Classifications of Intellectual Disability Severity. From National Academies of Sciences, Engineering, and Medicine. 2015. Mental Disorders and Disabilities Among Low-Income Children[64]. https://doi.org/10.17226/21780. Reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington D.C.
AAIDD, American Association on Intellectual and Developmental Disabilities; DSM, Diagnostic and Statistical Manual of Mental Disorders; IQ, Intelligence Quotient.

TABLE 9-1 Classifications of Intellectual Disability Severity

Severity Category	Approximate Percent Distribution of Cases by Severity	DSM-IV Criteria (severity levels were based only on IQ categories)	DSM-5 Criteria (severity classified on the basis of daily skills)	AAIDD Criteria (severity classified on the basis of intensity of support needed)	SSI Listings Criteria (The SSI listings do not specify severity levels, but indicate different standards for meeting or equaling listing level severity.)
Mild	85%	Approximate IQ range 50–69	Can live independently with minimum levels of support.	Intermittent support needed during transitions or periods of uncertainty.	IQ of 60 through 70 *and* a physical or other mental impairment imposing an additional and significant limitation of function
Moderate	10%	Approximate IQ range 36–49	Independent living may be achieved with moderate levels of support, such as those available in group homes.	Limited support needed in daily situations.	A valid verbal, performance, or full-scale IQ of 59 or less
Severe	3.5%	Approximate IQ range 20–35	Requires daily assistance with self-care activities and safety supervision.	Extensive support needed for daily activities.	A valid verbal, performance, or full-scale IQ of 59 or less
Profound	1.5%	IQ <20	Requires 24-hour care.	Pervasive support needed for every aspect of daily routines.	A valid verbal, performance, or full-scale IQ of 59 or less

1.8 BEHAVIOURAL AND EMOTIONAL DIFFICULTIES, SLEEP, AND QUALITY OF LIFE

1.8.1 BEHAVIOURAL AND EMOTIONAL DIFFICULTIES

Behavioural and emotional difficulties in children can lead to negative personal outcomes and diminished QoL[65]. Difficulties can lead to poor integration, exclusion from school, limit friendships, and interfere with learning and development[66, 67]. Children with intellectual disability are a particular risk group for experiencing emotional and behavioural difficulties[68, 69].

Children with emotional and behavioural difficulties may reach the criteria for particular diagnoses which may be described as mental health or psychiatric diagnoses. Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are typically considered neurodevelopmental disorders[63]. Common mental health and psychiatric diagnoses in children include anxiety, depression, oppositional defiant disorder and conduct disorder. Diagnosing these disorders in children with ID, particularly moderate or severe level of ID, may be challenging as there are few well validated instruments for this population[70, 71].

Behavioural and emotional difficulties such as anxiety, depression, hyperactivity, and inattention are common in children with epilepsy[72-74]. These difficulties are more common in children with epilepsy compared with children without epilepsy [75, 76], or children with other chronic health conditions such as diabetes[77] and asthma[78]. It has been concluded that an underlying neurological dysfunction can cause both seizures and behavioural problems[79]. suggesting that it is not epilepsy per se, but the underlying cause of epilepsy which drives both seizures and at least some of the behavioural and emotional problems.

The frequency of behavioural and emotional problems is higher in DS than in the normal population and in individuals with a *SCN1A* variant, who do not fulfil criteria for DS[10]. Individuals with DS had a higher frequency of somatic problems, attention problems, aggressive behaviour, and total behavioural problems compared with the general population and with individuals with *SCN1A* related seizures, that did not fulfil DS criteria[10]. They also had a significantly higher frequency of withdrawn behaviour compared with the

general population[10]. Another study highlighted that common behavioural problems in DS are inattention, hyperactivity, conduct problems, and problems with peer relationships[8].

It is important to use instruments that are adapted to children with ID when investigating behaviour in DS, as moderate or more severe ID is seen in the majority of children[9]. Many of the commonly used instruments to measure behaviour and emotions in children such as the Child Behavior Checklist (CBCL)[80, 81], or Strengths and Difficulties Questionnaire (SDQ)[82] are less reliable for children with moderate or lower levels of ID[83, 84]. In particular items which focus on behaviours or emotions associated with intact verbal ability (e.g., lying, use of swear words) may not be suitable for children with ID. There are also behaviours seen in children with severe to profound ID that are uncommon in other children and might be overlooked when using the instruments designed for children without ID, especially self-absorbed behaviour, such as eating non-food, humming and grunting[69, 83, 85]. Additionally, it can also be difficult to decide whether some behaviours (e.g., difficulties with attention) separate from ID[69, 85].

Ninety-five percent of caregivers of children with DEEs felt that evaluating behaviour and emotions is important, according to one study[86], but the majority felt that the difficulties were not appropriately assessed, highlighting the need to use methods valid for this population.

1.8.2 SLEEP

Problems related to sleep such as night waking, parasomnias, sleep disordered breathing, and reduced sleep efficiency are more common in children with epilepsy, compared with children without epilepsy[87]. Rapid eye movement (REM) sleep is reduced in children with drug-resistant epilepsy compared to other children with epilepsy[88]. REM sleep might be important for consolidation of emotional and procedural memory, i.e., the process of retrieving information necessary to perform learned skills such as riding a bicycle[88, 89]. Slow wave sleep or stage 3 of non-rapid eye movement (NREM) sleep has been shown to play a role in hippocampus-dependent declarative memory, i.e., conscious memory such as recollection of facts and events[88, 89].

A reduction of REM sleep has been observed the night following a seizure[90, 91]. Seizures at night, but not during the day, reduced sleep efficiency and slow wave sleep and increased drowsiness in one study[90]. Disturbance of sleep architecture by seizures and/or interictal epileptic activity might have a role in cognitive stagnation in DEE, and treatment of sleep-related problems might positively affect cognitive outcome[92]. A high load of interictal epileptic discharges during slow wave sleep are associated with poorer memory performance both in focal epilepsy due to a structural lesion and in self-limited focal epilepsies[93, 94].

Sleep-related problems are reported in 42-97% of individuals with DS[11-15]. Problems initiating and maintaining sleep, sleep-wake transition disorders, sleep breathing disorders and use of sleep-inducing medications have all been identified in 30-40% of individuals with DS[12].

Severe sleep-induced problems in individuals with DS have been reported by 28% of their caregivers and were mainly related to night waking or daytime sleepiness in a Dutch study[14]. In this study there were no significant differences compared with a control group of children with epilepsy, except that day-time sleepiness was more common in the DS group.

1.8.3 QUALITY OF LIFE

The World Health Organization (WHO) has defined QoL as `an individual´s perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns´[95]. This definition is based on a shared understanding of the concept `QoL´ by researchers as subjective, multi-dimensional, and including both positive and negative aspects of life, and has been confirmed by focus groups of patients, healthy individuals, and health care professional in different cultural settings[95].

The HRQoL concept was developed to capture subjective experience related to health, disease, disability, and impairment and the effects of medical treatment[96, 97]. There are many different definitions, but two central aspects found in most definitions, are that HRQoL is subjective and thus should be assessed from the individual's perspective and that HRQoL is a multi-dimensional concept addressing at least physical, mental, and social domains

of health[96, 97].The terms health, HRQoL and QoL are key terms for evaluation of interventions and to influence decisions about patient care, but the definition of each term varies and they are used interchangeably in the literature[96, 98-100].

Subjective views regarding health, HRQoL and QoL reported directly by the patient, have been considered important the last 20 years[97, 102]. Consequently, a child should ideally be questioned themselves about QoL and HRQoL as evaluation of these concepts might differ between children and their caregivers[96, , 101]. Self-reported QoL or HRQoL is complicated or impossible in children with moderate or severe ID. Consequently, in most children with DS, one must rely on proxy-reports by caregivers. The majority of instruments that can be used in children and adolescents are disease specific, but there are also some generic instruments, i.e., instruments that can be used to measure HRQoL in different diseases and also in the general population[103]. Some of those generic instruments are reliable, valid and sensitive and have been validated in different cultural settings[103]. When using HRQoL, there is a risk of attributing QoL to health status without consideration of other influences on how people value their QoL such as social and personal resources and limitations[99].

One of few instruments measuring HRQoL developed for children with ID and epilepsy is the ELDQOL[104]. The measure provides scores for four subscales but no overall composite of QoL score. Recently, new QoL scales for children with ID have been made available in English[105, 106], but there are to our knowledge, currently no well-used measure of QoL in children with epilepsy and ID that provides an overall composite QoL value.

In one study on DS, individuals with the highest current seizure frequency had lower QoL and more comorbidities compared with individuals with the lowest seizure frequency[107].

2 AIMS

- To identify all Swedish children with DS born between January 1, 2000, and December 31, 2018, in a population-based study (Paper I).

- To describe epidemiology, genetic profile, mortality, seizure-burden, and treatments in children with DS (Paper I).

- To describe caregiver-reported seizure-provoking factors and strategies to reduce seizures and their consequences in children with DS (Paper II).

- To assess intellectual function and adaptive behaviour in children with DS (Paper III).

- To describe behavioural problems, insomnia and QoL in children with DS (Paper IV).

3 PARTICIPANTS AND METHODS

3.1 PARTICIPANTS AND INCLUSION

This is a cross-sectional, population-based study of Swedish children with DS. To identify children with DS we used a register from an earlier study[108]. Additionally, all members of the support organisation Dravet Syndrome Association Sweden were informed about the study by their association. Swedish neuropaediatricians and epilepsy nurses were approached in national meetings and personally to investigate if they treated any children with DS. If so, they were asked to inform the caregivers about the study.

All children born between January 1st, 2000, and December 31st, 2018, who fulfilled inclusion criteria were invited to participate in the study. We used inclusion criteria described by Nabbout et al.[37]: a) A normal EEG and normal development until the first seizure; b) The first seizure appearing before one year of age; c) Refractory clonic or tonic-clonic seizures affecting one or both sides simultaneously or alternatively; d) No pre-existing cerebral lesion; e) Exclusion of any other identified epilepsy syndrome including negative *PCDH19* analysis in participants without a *SCN1A* variant that could explain DS.

New ILAE criteria for DS[1] could not be used as they were published after this study was started. The children were examined between October 15th, 2018 and April 3rd, 2020 at the Queen Silvia Children´s Hospital in Gothenburg or at their home hospitals. One child was assessed at home due to Covid-19 restrictions.

We identified 55 children born between 1/1 2000 and 31/12 2018, who fulfilled inclusion criteria, 29 (53%) were males and 53 (96%) were born in Sweden. The recruitment process is described in Figure 5. Thirty-two children were recruited from a register from a previous study[108], 20 were recruited by neurologists and the caregivers of three children contacted the research team. All these three children were followed by a paediatric neurologist and had a DS diagnosis. Seven children were deceased and thus 48 living children had DS in Sweden on December 31st, 2018.

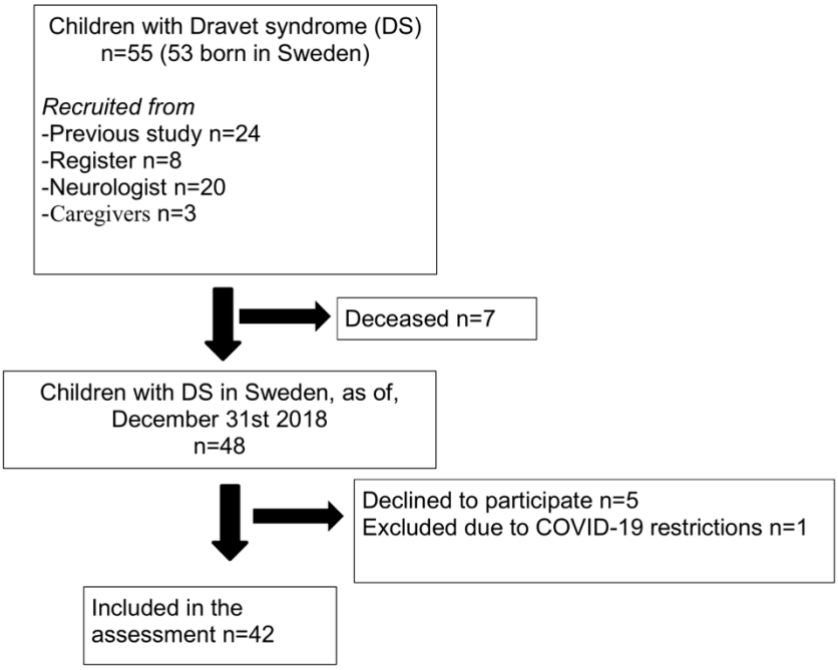

Figure 5. Recruitment for 55 Swedish children with Dravet syndrome. From Paper I. Copyright 2022 the authors.

Caregivers of 42 children agreed to participate in an extended assessment on clinical factors regarding epilepsy, behaviour, sleep, QoL and cognition (Paper I-IV). Clinical data were compared between two age groups: 18/42 `older´ children born 2000-2009 and 24/42 `younger´ children born 2010-2018 (Paper I-IV). Epilepsy severity defined as `severe´ or `less severe´ was based on median split and was explored using five questions from the ELDQOL scale[104], previously used in another study[8] (Paper II-IV).

In agreement between BB and TH, one child with a pathogenic *SCN1A* missense variant and typical features of DS, including ID, atypical absences, and myoclonic seizures, was included in the study even though two of the inclusion criteria were not fulfilled. The child had the first reported seizure at

the age of 2.3 years and a benign infra-tentorial tumour, that was not considered causal of the DEE.

3.2 STATISTICAL ANALYSES

A Chi square test was used to compare current and previous use of sodium channel inhibitors, and presence of different seizure types in `younger´ compared to `older´ children (Paper I). A Chi square or Fisher´s exact test was used to compare the frequency of different precipitants and measures to avoid seizures in children with severe´ and `less severe´ epilepsy and `younger´ and `older´ children (Paper II).

A Mann Whitney U test was used to compare the age at DS diagnosis and age at *SCN1A* testing between `younger´ and `older´ children (Paper I), and to compare number of reported seizure precipitants and preventive measures the last three months, and frequency of rescue medication used the last three months, between `older´ and `younger´ children, and between children with `severe´ and `less severe´ epilepsy (Paper II).

Comparisons between domains on Vineland Adaptive Behavior Scales – Second Edition (VABS-II) and indexes on Wechsler tests were undertaken with paired sample *t*-tests (Paper III). Wilcoxon signed rank test was used to compare scores between different subscales in the Developmental Behavior Checklist (DBC) (Paper IV). We used parametric and non-parametric tests as appropriate.

Logistic regression was used to identify if specific clinical factors (predictors) were associated with severe ID (Paper III). Linear regression was used to identify if specific clinical factors were associated with adaptive behaviour (Paper III), and with behaviour, sleep and QoL (Paper IV). The possible predictors analysed for in regression models are described in Table 2. All predictors for both linear and logistic regression were first tested in an univariable analysis and predictors correlated at the $p < 0.200$ level were included in the multivariable modelling, as previously described[109]. The IBM SPSS Statistics version 28 (IBM Corporation, Armonk, NY, USA) was used for the statistical analyses.

Table 2. Possible predictors analysed in regression models in Papers III and IV.

Dependent variable/method	Possible predictors analysed
Severe ID/ logistic regression in Article III	Sex (male/ female), previous use of contra-indicated sodium channel inhibitor (yes/no), type of *SCN1A* mutation (truncating or missense), age category (younger vs older based on median split), epilepsy severity[a] (based on median split), age at ASM start (median split), age of first episode of convulsive SE (median split), autism status (at-risk/not at risk)[b], age of first seizure (median split).
Adaptive behaviour[c]/ linear regression in Article III	Sex, age at assessment (years) age at first seizure (years), age at first episode of convulsive SE (years), age at first ASM (years), previous use of sodium channel inhibitor (yes/no), epilepsy severity[a] (based on median split), autistic symptoms[b](score), type of *SCN1A* mutation (truncating or missense).
Behaviour, insomnia, and QoL/ linear regression in Article IV	Sex, age at assessment (years), age at first seizure (years), age at first episode of convulsive SE (years), previous use of sodium channel inhibitors, epilepsy severity[a] (based on median split), severity of side effects associated with ASMs[d] (score), adaptive behavior[c] (score), if the child had severe ID (yes or no), autistic symptoms[b] (score). Composite scores of DBC and ISI were included as possible predictors of QoL and composite score of DBC and ISI were included as possible predictors for each other.

Based on five items from the ELDQOL scale as previously described[8]. [b]Based on results of the Social Communication Questionnaire (SCQ) total score. [c]Based on Vineland Adaptive Behavior Score – Second Edition. [d]Based on the ELDQOL subscale `Side effects´. ASM, Anti-seizure medication; DBC, Developmental Behavior Checklist; ELDQOL, Epilepsy and Learning Disabilities Quality of Life; ID, Intellectual disability; ISI, Insomnia Severity Index; QoL, quality of life; SCN1A, gene encoding the sodium voltage-gated channel type 1 alpha subunit, SE, status epilepticus.

A p-value <0.05 was considered statistically significant, even when multiple tests were performed. DS is an uncommon epilepsy syndrome where little is known regarding the areas that we studied, and the number of individuals that were available for a population-based study were relatively few. Thus, it was

not possible to use a deductive approach with testing of hypotheses. Instead, we chose to use an inductive, explorative approach with the aim to build hypotheses that should be tested in larger studies. To be able to use our data efficiently, it was important to avoid false negative type II errors.

3.3 PAPER I AND II

3.3.1 THE CASE REPORT FORM

In paper I, II and III we used a Case Report Form (CRF). We used the same CRF for paper I and III (Appendix 1) and a modified CRF for Paper II (Appendix 2). Clinical data regarding seizure types and treatments (Paper I) and seizure provoking factors according to caregivers and strategies to avoid seizures and prolonged seizures (Paper II) were collected in a semi-structured, face-to face interview with caregivers.

Caregivers of 42 children participated in the interview. This interview was based on the CRF, supplemented with information from the medical records. The questions in the CRF were developed based on clinical experience and earlier studies[11, 110].

3.3.2 PAPER I

In this paper we describe cumulative incidence, prevalence, mortality, frequency of variants in the *SCN1A* gene, seizure types and epilepsy treatment in DS.

Cumulative incidence was calculated on the 53 children born in Sweden with reference to all children born in Sweden between 2000 and 2018. Prevalence was calculated on the 48 living children with DS (including two children born abroad) with reference to the present population of children living in Sweden, who were born between 2000 and 2018. Mortality and age at *SCN1A* analysis were extracted from medical records, the caregivers informed about age at DS diagnosis, and these data were analysed on 53 children born in Sweden.

Based on the CRF (Appendix 1), previous and ongoing seizure types within the last three months and epilepsy treatments were analysed on the 42 children.

Seizure types were classified according to current ILAE classification[111], based on description of semiology by caregivers.

We defined SE as a convulsive or non-convulsive seizure lasting at least 30 minutes, or a sequence of convulsive seizures lasting at least 30 minutes without regain of consciousness between seizures[112, 113]. SUDEP was classified according to criteria developed by Devinsky et al.[114]: If no other causes of death had been found, the death was classified as `definite´ in cases with autopsy and as `probable´ in cases without autopsy. The death was classified as `possible´, where there were other possible causes of death.

3.3.3 PAPER II

Based on clinical data in the CRF (Appendix 2) we described caregiver reported seizure precipitants and measures to prevent seizures and their consequences in the 42 children who took part in the extended assessment.

3.4 PAPER III

In Paper III we describe the results of comprehensive psychological assessments, that was performed by an experienced psychologist (Colin Reilly). DSM-5 criteria were used for research diagnosis of ID[63]. Forty-two children took part in this assessment. One child with a previous ID diagnosis could not be re-tested by our psychologist due to illness. In the current study this child's level of ID was based on the result of the assessment of the adaptive behaviour interview conducted with the child´s caregiver. The following instruments were used:

• Wechsler scales[115-117] for assessment of cognition (n=11). Age-appropriate instrument was used, i.e., Wechsler Preschool and Primary Scales of Intelligence – Fourth Edition (WPPSI-IV), Wechsler Intelligence Scale for Children – Fifth Edition (WISC-5) or Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV).

• The Griffiths Mental Development Scales – Third Edition[118] for assessment of developmental functioning. This instrument was used for children younger than 2.5 years (n=1) or a with a low level of intellectual functioning (n=29).

• Vineland Adaptive Behaviour Scales – Second Edition (VABS-II)[119] for assessment of adaptive behaviour in four domains: Communication, Daily Living Skills and Motor skills. The motor domain was only used for children younger than seven years. The caregiver(s) were interviewed.

• The Social Communication Questionnaire (SCQ), previously known as the Autism Screening Questionnaire is a validated screening instrument for ASD, consisting of 40 yes/no questions, associated to symptoms of ASD[120, 121]. The SCQ is based on ICD-10 and DSM-IV criteria for autism and has a recommended cut-off of 15 or higher for both verbal and nonverbal participants to determine at risk status[120, 121].

3.5 PAPER IV

Behaviour, sleep and QoL were assessed using standardised questionnaires answered by caregivers. We used the following instruments:

• The Developmental Behavior Checklist – Second Edition (DBC-2) – for assessment of behaviour and emotional difficulties in children with mild to profound ID, including those with co-occurring ASD[85, 122, 123]. In our study we had six children without ID. In scoring they were counted as mild ID, as DBC-2 is only validated for children with ID. DBC-2 consists of 96 descriptions of behaviour and norms, and is available for mild, moderate, severe, and profound ID and for the ID group as a whole. Each item is scored on a 3-point scale: Not true as far as you know (0), sometimes or somewhat true (1), often true or very true (2). All items are added to give a total behaviour raw score. The raw scores can be converted to standardised T scores (DBC-T scores) which makes it possible to compare scores in the different subscales.

We used the revised DBC-P (parent form) adapted for evaluation of children 4-18 years old. There are five subscales representing clinically relevant dimensions of behaviour among children with ID: self-absorbed; disruptive; communication disturbance; anxiety and socially relating. The DBC subscales have been shown to be reliable and valid measures of caregivers´ ratings of behavioural disturbances and the subscales have high factorial validity and internal consistency[122]. The total score has high validity shown by correlations between the scale and psychiatrists´ classification and with other valid instruments assessing behavioural disorders in children with ID.

There are three ranges of concern displayed for the total score and for the sub-scores. A T-score <40 indicates a range of `little´ concern, a T-score of 40-50 indicates a range of `moderate´ concern and a T-score >50 indicates a range of `serious´ concern. An overall score that falls into the range of `serious´ concern indicates behavioural and emotional problems that require management or treatment and further assessment[123]. Individuals with an overall range of `serious´ concern are more likely to meet the criteria for a mental health diagnosis. A score of `moderate´ concern might indicate problems that require management or treatment and meet the criteria for a mental health diagnosis.

The Insomnia Severity Index (ISI) – for assessment of the nature, severity and impact of sleep difficulties[124]. ISI describe the prevalence of sleep difficulties and factors associated with those difficulties. It is composed of seven items, assessing recent problems with sleep onset, sleep maintenance, early morning awakening, sleep dissatisfaction, noticeability of sleep problems by others, interference of sleep difficulties with daily functioning, and distress caused by sleeping difficulties. The current severity (i.e., last two weeks) of each item is rated on a 5-point Likert scale: No problem (0); mild problem (1); moderate problem (2); severe problem (3) and very severe problem (4). This yields a total score ranging from 0 to 28. Total scores are interpreted as follows: absence of insomnia (0–7); sub-threshold insomnia (8–14); moderate insomnia (15–21); and severe insomnia (22–28).

The questionnaire showed adequate concurrent validity with sleep diaries and polysomnography and adequate internal consistency and could detect changes in perceived sleep difficulties when used in adults[124]. The ISI has typically been used as a self-report questionnaire in adults, but has also been used to measure insomnia evaluated by caregivers in children with cerebral palsy[125], and as a self-report instrument in children with chronic pain[126] and obsessive–compulsive disorder[127]. Cronbach's alpha, a measure of internal consistency was 0.89 in Paper IV for the ISI subscales and could thus be considered good[128]. We modified the ISI as a proxy instrument for children, by exchanging the word `you´ with `your child´, as there were no validated scales to evaluate sleep-related problems for children available in Swedish at the time of the study[129]. In our study, we define `insomnia´ as sleep-related problems scored with the ISI.

One global question from Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale – a measure of QoL in children with epilepsy and ID[104]. The question is `How would you describe the QoL of your child during the last four weeks?´. The question is rated on a 5-point Likert scale from `Very good´ to `Very bad´. A similar single question from the Quality of Life in Childhood Epilepsy Questionnaire- the 76-item parent rated instrument (QOLCE-76)[130] `In the past 4 weeks, what has your child's QoL been´ has been rated on a five-point Likert scale from `Excellent´ to `Poor´. This question has been validated for evaluation of QoL in children with focal, drug-resistant epilepsy[131]. It had moderate test-retest reliability, was able to detect clinically important changes in patients' QoL and showed moderate to strong correlations ($r \geq 0.30$-0.50) with the composite scores in KIDSCREEN-27[132] and QOLCE-76[133].

Subscales of the full ELDQOL scale have shown good reliability and validity when used in children with ID and severe epilepsy[104]. It is not possible to derive a total score of QoL, from this scale. There are, to our knowledge, currently not any widely used or accepted scales for HRQoL or QoL in children with epilepsy and ID. Those that are widely used, such as QOLCE or PedsQL have items not suitable for children with ID.

3.6 ETHICAL CONSIDERATIONS

The study was approved by the Ethical Review Committee of the University of Gothenburg (Sweden) and The Swedish Ethical Review Authority (Dnr 450-10, T672-18, and 2020-03783). Written informed consent was obtained from caregivers and from two participants older than 15 years who were developmentally able to understand information about the study.

This study identified the extent of cognitive, behavioural, and epilepsy-related difficulties in children with DS and the extent of the impact on daily life that DS has. This might lead to negative emotions and reactions in children and their caregivers. In such cases, support was available from the psychologist in the research team, to explain results of assessments and advise on accessing support.

The study is undertaken from the perspective of the caregivers, which is of importance as caregivers can identify impact on their children and themselves not reported by healthcare professionals[134]. Understanding the extent of these

factors and the impact on caregivers is essential to optimise healthcare and quality supports from social care and the educational system, which can be beneficial for the caregivers and children participating in this study.

Another ethical dilemma is that in a small population-based study it might be possible to identify individual families and children, particularly by caregivers to other children with DS. However, all analyses are undertaken at the group level and every effort is made to ensure that individual children cannot be identified.

4 RESULTS AND DISCUSSION

4.1 DRAVET SYNDROME IN CHILDREN — A POPULATION-BASED STUDY (PAPER I)

In Paper I we describe prevalence, demography, mortality, genetics, seizure types, and anti-seizure treatments in Swedish children with DS.

4.1.1 An increased discovery rate of DS with a narrower phenotype?

The cumulative incidence in `younger´ children (1:33,000) was higher than in `older´ children (1:46,000, p=0.03). The median age at DS diagnosis (1.6 versus 4.5 years, p=0.001), and *SCN1A* analysis (1.3 versus 4.7 years, p<0.001) was lower for `younger´ children. Less contra-indicated sodium-channel inhibitors had been used in `younger´ compare with `older´ children (9/24 versus 17/18, p=0.001). These data are presented in Table 3.

We found 48 children in Sweden, corresponding to a prevalence of 1:45,000 (95% confidence interval (CI) 1:35 000-1:63 000). The prevalence in a previous Swedish study[108] published in 2015 was similar (1:46,000), even though seven out of 31 children who also participated in that study, did not fulfil the DS criteria in our study. Of the seven children, who did not fulfil our inclusion criteria, four had a phenotype compatible with GEFS+, one had an extensive deletion, containing the entire *SCN1A* gene, and a more severe phenotype than DS, and two children had variants in other genes than the *SCN1A* gene.

Among participants in our study, 51/53 (96%) children with known *SCN1A* status had a *SCN1A* variant that could explain DS. In the previous Swedish study[108], 88% had this type of *SCN1A* variant, and in studies published before 2013, less than 80% had a *SCN1A* variant that could explain DS[6, 135, 136].

The findings above indicate an increased diagnostic awareness of DS over time, leading to an increased identification of individuals with DS, despite of a changed and narrower definition of DS[137]. Disease definition, genetic

identification, and diagnose-specific treatment approval all are factors that lead to increased awareness of rare diseases like DS[137].

Table 3. Cumulative incidence increased, age at Dravet syndrome (DS) diagnosis and SCN1A analysis decreased and use of contra-indicated ASMs decreased in `younger´ Swedish children with DS, indicating an increased knowledge of DS. Modified from Paper 1. Copyright 2022 the authors.

Variable	Born 2000-2009	Born 2010-2018	P
Cumulative incidence[1]	1/46,000	1/33,000	0.03
95% confidence interval	1/32,000-1/79,000	1/24,000-1/51,000	
n	22	31	
Age at DS diagnosis[1]			
Median (range)	4.5 (1.0-10.0)	1.6 (0.5-5.0)	0.001[2]
n[3]	21	27	
Age at *SCN1A* analysis[1]			
Median (range)	4.7 (0.86-13)	1.3 (0.40-4.0)	<0.001[2]
n[4]	18	23	
Use of contra-indicated Sodium-channel inhibitors[5]			
n (%)	17/18 (94)	9/24 (38)	0.019[6]

ASMs, Anti-seizure medications; DS, Dravet syndrome; SCN1A, Gene encoding the sodium channel alpha subunit type 1. [1]Calculated for children born in Sweden (n=53). [2]Mann Whitney U-test. [3]Age at DS diagnosis was not known for five children [4]Age at SCN1A analysis was not known for 10 children, and 2 children did not have a SCN1A variant. [5]Calculated for 42 children who participated in an extended assessment. [6]Chi square test.

Easier access to and improved quality of genetic testing in the last 20 years[138] can also lead to that DS is identified on basis of the finding of a *SCN1A* variant, in individuals where the diagnosis was not initially suspected. In relation to the finding of a lower cumulative incidence in `older´ compared with `younger´ children, there may be a tendency to accept the diagnostic work that already has been done in children who got an epilepsy diagnosis several years ago, before DS was well described.

4.1.2 MORTALITY

Among the 53 children born in Sweden seven (13%) had died. One child died of seizure-induced aspiration leading to acute anoxic brain injury. One child

died of `definite´ SUDEP. Two died of `probable´ or `possible´ SUDEP associated with pneumonia or pneumonitis. Three died of complications related to pneumonia or pneumonitis with no indications of co-excising SUDEP. Thus, in five out of seven deaths the mortality was associated with pulmonary infections. This is higher than previously described[4, 5].

We used the classification of SUDEP described by Devinsky and co-workers[114]. Another term used in this classification is `SUDEP plus comorbidity´, where a concomitant condition may have contributed to the death but was unlikely an independent cause of death. Due to limited information regarding mortality in medical records we considered it difficult to differ between `possible´ SUDEP and `SUDEP plus comorbidity´. Thus, we chose to use the term `possible´ SUDEP or `probable´ SUDEP also for possible `SUDEP plus´ cases. The two cases described as possible/probable SUDEP with simultaneous pulmonary infection, might have been classified as probable/definite `SUDEP plus´[114]. The relationship between SUDEP and pulmonary infections, were described as an area of uncertainty and disagreement in the review of SUDEP cases by Devinsky and co-workers[114].

4.1.3 SEIZURE TYPES

All 42 children had ongoing seizures, with seizures within the last three months, according to caregivers. They had experienced a median of 4.5 (range 1-6) seizure types asked for and had a median of 3 (range 1-6) seizure types within the last three months. Frequency of different seizure types are presented in Table 4. Focal to bilateral tonic clonic seizures had been experienced by 41/42, (98%), myoclonic by 35/42, (83%), focal by 34/42 (81%), absence by 33/42 (79%), tonic by 25/42 (60%), and atonic seizures by 15/42 (36%). There was no significant difference in frequency of different seizure types between `older´ and `younger´ children. Febrile seizures had been experienced by all, convulsive SE by 38/42 (90%) and non-convulsive SE by 14/42 (33%). The participants in this study had a very heavy seizure burden, in line with results in other studies[58]. Tonic seizures were more common than previously described[19, 139-141], and there was no difference in frequency of this seizure type in `younger´ compared with `older´ children.

Table 4. Seizure types in 42 children with Dravet syndrome[#]. Modified from Paper I. Copyright 2022 the authors.

Seizure type	Ongoing seizures		Observed previously	Not observed	Missing data
	n (%)	Frequency[1] Median (range)	n (%)	n (%)	n (%)
Focal to bilateral tonic-clonic	37 (88)	3.0 (0–680)	4 (9.5)	0	1 (2.4)
Focal	22 (52)	6.0 (0–200)	12 (29)	6 (14)	2 (4.8)
Tonic	16 (38)	2.5 (0–220)	9 (21)	15 (36)	2 (4.8)
Atonic	6 (14)	7.5 (1–360)	9 (21)	25 (60)	2 (4.8)
Myoclonic	22 (52)	Uncountable	13 (31)	6 (14)	1 (2.4)
Absence	26 (62)	Uncountable	7 (17)	7 (17)	2 (4.8)
Status epilepticus[2]					
Convulsive	38 (90)	9 (1–50)[3]	N/A	4 (9.5)	0
Non-convulsive	14 (33)	32 (1–200)[4]	N/A	26 (62)	2 (4.8)

[#]Caregivers were given a description of the different seizure types and were then asked if the child currently displayed or had previously experienced the described seizure types.
N/A, not applicable.[1]Frequency of seizures was estimated by the caregivers as the mean number per month the last 3 months. The frequency of status epilepticus was estimated as the total number of episodes during the lifetime.
[2]Status epilepticus was defined as a seizure that lasted at least 30 minutes, or as repetitive convulsive seizures that lasted at least 30 minutes without recovery of consciousness.[3]Episodes that exceeded 50 in number were not counted.[4]Episodes that exceeded 200 in number were not counted.

4.1.4 ANTI-SEIZURE TREATMENTS

The most common ASMs in current use were valproate (n=32/42, 76%), benzodiazepines (clobazam, clonazepam, or nitrazepam) (n=31/42, 74%), stiripentol (n=13/42, 31%) and topiramate (n=12/42, 29%). A combination of valproate and benzodiazepines were used by 15/42 (36%), and a combination, of valproate, benzodiazepines and stiripentol in another 9/42 (21%). Thus, most children used ASMs recommended for DS[49]. None of the children in our study used fenfluramine and only three had used cannabidiol. These ASMs are currently not subsidized in Sweden and consequently, are rarely used.

Four children (9.5%) currently used sodium-channel inhibitors. Interestingly, one of the four children, with a large duplication in the *SCN1A* gene, had a seizure reduction of >50% when starting the sodium-channel blocker lacosamide. Deterioration in seizure control when taking away sodium-channel blockers in DS has been described in some case reports[142, 143].

4.1.5 CONCLUSION

- Cumulative incidence was higher, age at DS diagnosis lower and less children had used contra-indicated sodium-channel blockers in the `younger´ age group indicating an increased awareness of DS.

- In our study 96% had a *SCN1A* variant that could explain DS. The amount of *SCN1A* positive individuals with DS seems to gradually have increased over time, indicating better genetic assessments.

- In our study seven out of 53 (13%) children born in Sweden had died. This mortality rate is in line with previous studies. The majority had a mortality associated with pulmonary infections. This is higher than previously described[4, 5].

- Tonic seizures were described in 25/42 (60%). This number of tonic seizures is higher than in previous studies[140, 141].

4.2 CAREGIVER REPORTED SEIZURE PRECIPITANTS AND MEASURES TO PREVENT SEIZURES (PAPER II)

4.2.1 SEIZURE PRECIPITANTS

Seizures had according to caregivers been provoked by at least two factors in all children. They were currently provoked by a median of seven (range 0-11) out of 13 factors asked for. Different seizure precipitants are presented in Table 5.

Table 5. Caregiver reported total and current seizure precipitants out of 13 possible in 42 children with Dravet syndrome Modified from Paper II. Copyright the authors.

Factor	Total	Current	No	Unknown
Infection with fever	42 (100)	37 (88)	0	0
Afebrile infections	39 (93)	28 (67)	2 (4.8)	1 (2.4)
Physical activity	35 (83)	27 (64)	6 (14)	1 (2.4)
Tiredness	32 (76)	29 (69)	8 (19)	2 (4.8)
Warm weather	29 (69)	26 (63)	11 (27)	2 (4.8)
Strong emotions	27 (64)	25 (60)	15 (36)	0
Sleep	25 (60)	23 (55)	16 (38)	1 (2.4)
Crowds	22 (52)	19 (45)	16 (38)	4 (9.5)
Reduced ambient temperature	20 (48)	18 (43)	20 (48)	2 (4.8)
Bright light	19 (45)	16 (38)	20 (48)	3 (7.1)
Noise	11 (27)	10 (24)	31 74)	0
Geometric patterns	10 (24)	9 (21)	32 (76)	0
Other factors	10 (24)	8 (19)	29 (69)	3 (7.1)

Seizures were attributed to increased internal or external temperature such as fever, physical activity, and warm weather and by emotional factors such as tiredness, strong positive or negative emotions and being exposed to crowds. Seizures were also reported to be provoked by other factors such as infections without fever and sleep. Increased internal or external temperature, emotional factors and having a cold were commonly reported seizure triggers also in a Dutch study of children and young adults with DS[7]. In the Dutch study, 99% reported at least one seizure precipitant, and precipitants were more commonly reported in individuals with DS than in a cohort with children with other types of epilepsy and a community-based cohort with epilepsy.

Interestingly a total of 20/42 (48%) children had, according to caregivers, seizures provoked by reduced temperature, such as taking a cold bath. To our knowledge this has not been described previously. This might be an expression of the hyperexcitability described in DS[61].

Afebrile infections were more commonly reported as seizure precipitants in `younger´ children (n=20/24, 83%) compared to `older´ children (n=8/17, 47%, p=0.014). This could be due to that viral respiratory tract infections are more common in `younger´ children[144]. Reduced ambient temperature also was reported to provoke seizures more commonly in `younger´ children (n=15/24, 62%) compared to `older´ children (n=3/16, 19%, p=0.006). A possible explanation could be that younger children lose temperature faster in a cold environment due to an increased body surface in relation to body weight[145].

Bright light was reported to provoke seizures more commonly in children with `severe´ epilepsy (n=12/20, 60%) than in children with `less severe´ epilepsy (n=4/19, 21%, p=0.013). In a study from Japan, constant bright light illumination provoked seizures more frequently in six younger children with the most drug-resistant epilepsy with very frequent myoclonic and absence seizures[56]. In this study sensitivity to bright light illumination disappeared at around five years of age. In our study we could not see any significant difference in reported seizure provocation by bright light between `younger´ and `older´ children (n=9/22 (41%), vs n=7/17 (41%), p=0.99).

4.2.2 MEASURES TO PREVENT SEIZURES

All caregivers had taken measures to prevent seizures, `currently´ or `previously´. The different measures used, including measures to prevent temperature changes, limit emotions and infections, are presented in Table 6. A median of eight (range 0-17) measures were currently employed by caregivers to prevent seizures. There were several strategies used to avoid infections. One strategy was to increase hand hygiene for the child, family members, teachers, assistants, and other children in school/day-care. Other strategies were avoidance of individuals with infections by family members and avoidance of school/day-care by the child with DS and siblings in case of contagious infections. Antibiotic or intravenous immunoglobulin prophylaxis was also used in some children to avoid infections.

The number of current preventive measures was higher in children with `severe´ epilepsy (median 10) than in children with `less severe´ epilepsy (median 6, $p=0.031$). Crowds were currently more commonly avoided ($p=0.046$) and strategies to avoid infections ($p=0.024$), such as staying home if contagious infection in school/day-care ($p<0.001$), and family members avoiding infections ($p=0.009$)) were more commonly used in children with `severe´ epilepsy. Preventive measures and greater concern by caregivers are understandable in children with `severe´ epilepsy, since more severe seizures have greater effect on daily activities. Reduced temperature ($p=0.002$) was more commonly avoided in younger children. As we already have described, reduced temperature was more commonly reported as a seizure precipitant in younger children. Strong emotions were more commonly avoided ($p=0.035$) in younger children. Developmentally younger children may have stronger emotions but may also be easier to distract than older children.

Table 6. Number of total and current measures taken by caregivers out of 19 possible to prevent seizures in 42 children with Dravet syndrome[#]. Modified from Paper II. Copyright 2022 the authors.

Measures	Total	Current	No	Unknown
Avoid warm weather	35 (83)	33 (79)	7 (17)	0
Avoid physical activity	27 (64)	25 (60)	15 (36)	0
Avoid infections[1]	25 (60)	23 (55)[2]	16 (38)	1 (2.4)
Avoid tiredness	25 (60)	23 (55)	15 (36)	2 (4.8)
Avoid crowds	23 (55)	21 (50)	16 (38)	3 (7.1)
Avoid strong emotions	20 (48)	19 (45)	21 (50)	1 (2.4)
Avoid bright light	18 (43)	17 (40)	24 (57)	0
Avoid reduced temperature	15 (36)	15 (36)	25 (60)	2 (4.8)
Avoid patterns	9 (21)	9 (21)	33 (79)	0
Avoid noise	6 (14)	6 (14)	36 (86)	0
Avoid other factors	2 (4.8)	2 (4.8)	37 (88)	3 (7.1)
Stays home if infection in school/ day care	28 (67)	22 (52)	11 (26)	3 (7.1)
Sibling stays home if infection in school/day care[3]	16/34 (47)	11/34 (32)	17/34 (50)	1/34 (2.9)
Avoid infections- family members	26 (62)	24 (57)	15 (36)	1 (2.4)
Avoid infections- others[4]	17 (40)	16 (38)	22 (52)	3 (7.1)
Marquises used	19 (45)	18 (43)	23 (55)	0
Air condition used	19 (45)	17 (40)	23 (55)	0
Use of personal cooling device	22 (52)	22 (52)	15 (36)	5 (12)
Prophylaxis against infections[5]	10 (24)	7 (17)	32 (76)	0

[#]Caregivers were asked to describe different measures to avoid seizures. [1]Measures to avoid infections were performed for the child with DS. Caregivers were asked to describe how this was done. [2]Increased hand

hygiene (n=22), avoids individuals with infections (n=13), change clothes several times daily (n=1), shower after school (n=1). [3]In eight cases there were no siblings living in the same household. [4]Teachers, assistants, grandparents and/or other children in school/day-care performed measures to avoid infecting the child. [5]Intravenous immune-globulin or antibiotic prophylaxis.

4.2.3 MEASURES TO PREVENT PROLONGED SEIZURES AND THEIR CONSEQUENCES

Rescue medications had been used in all children and were currently used in 37/42 (88%) children. Rectal diazepam had been used by 39/42 (93%), buccal midazolam by 38/42, (90%) and nasal midazolam by 5/42 (12%). Nasal midazolam had recently been available in Sweden at the time of the study. Rectal diazepam is cheaper than buccal diazepam but can be harder to administer in older children and is also problematic in older children from an integrity perspective. Consequently, in Sweden, rectal diazepam is primarily given to preschool children.

Rescue medications had been used more frequently in the last three months in children with `severe´ epilepsy (median five, range 0-120) compared to children with `less severe´ epilepsy (median zero, range 0-75, p=0.007). These medications had also been used more frequently in `younger´ children (median five, range 0-120), compared to `older´ children (median zero, range 0-12, p=0.006). This finding is in line with previous studies and could indicate that the frequency of SE, decrease gradually after two years of age[21], that the overall seizure frequency decrease with age[107], and that seizures tend to be less severe after five years of age[19].

Home pulse oximetry had been used by 13/42 (31%) children to detect seizure-induced hypoxia, and home oxygen by 8/42 (19%) children to treat hypoxia, A Port-a-Cath had been inserted in 11/42 (26%) children to facilitate intravenous ASM treatment in case of SE. Frequent use of home pulse oximetry, home oxygen and Porth-a-Cath indicates a tendency to develop

severe, recurrent seizures that cannot be stopped with local administered benzodiazepines.

4.2.4 CONCLUSION

- Seizures were reported to be provoked by at least two factors in all children. This is in line with the results in a Dutch study[7]. Measures to prevent seizures had been used for all children. To our knowledge, such measures have not been described before in DS.

- Caregivers in this study described a range of different seizure provoking factors such an internal and external changes in temperature, strong emotions, and other factors such as infections without fever. These factors have to our knowledge, only been comprehensively described in one previous study[7].

- Seizures provoked by reduced ambient temperature were reported in almost 50% of children. This has, to our knowledge, not been described before.

- Rescue medications had been used in all children and were used more frequently in `younger´ children and children with `severe´ epilepsy. This is line with previous studies indicating that the frequency of SE decrease with age.

4.3 INTELLECTUAL FUNCTIONING AND ADAPTIVE BEHAVIOUR (PAPER III)

4.3.1 INTELLECTUAL FUNCTIONING

In paper III we present to our knowledge the first population-based study, investigating intellectual function, including adaptive behaviour in children with DS. Out of 42 children investigated, 4/42 (10%) had a normal cognitive function, 2/42 (5%) had a full-scale IQ of 70-84, and 36/42 (86%) fulfilled DSM-5 criteria for ID. Of those children, 12/42 (29%) had mild ID, 10/42 (24%) had moderate ID and 14/42 (33%) had severe ID (Figure 6). Our results are in line with a systematic review of 29 studies of cognitive function in children and adults with DS, with a total of 736 individuals, and an age range between 4 months and 60 years[9]. In the review, there was a pooled prevalence of 8% with a normal cognitive function (IQ>84), 6% with an IQ between 70

and 84 and 86% with ID. The frequency of mild ID was 22%, 26% had moderate ID and 38% had severe to profound ID. The results in our study confirm the results in the review, with between 80 and 90% with ID and a majority with moderate to severe ID.

Before the children were included in our study, only 28/42 (67%) children had an ID diagnosis and only 18/42 (43%) children had undergone a formal neuropsychological evaluation. The previous Swedish study, which is the only previous population-based study investigated intellectual function, was based on medical records and information from caregivers and not directly on comprehensive neuropsychological investigations[108]. In this study 28/42 (67%) had an ID diagnosis. These results highlight the importance of a comprehensive cognitive evaluation in all children with DS.

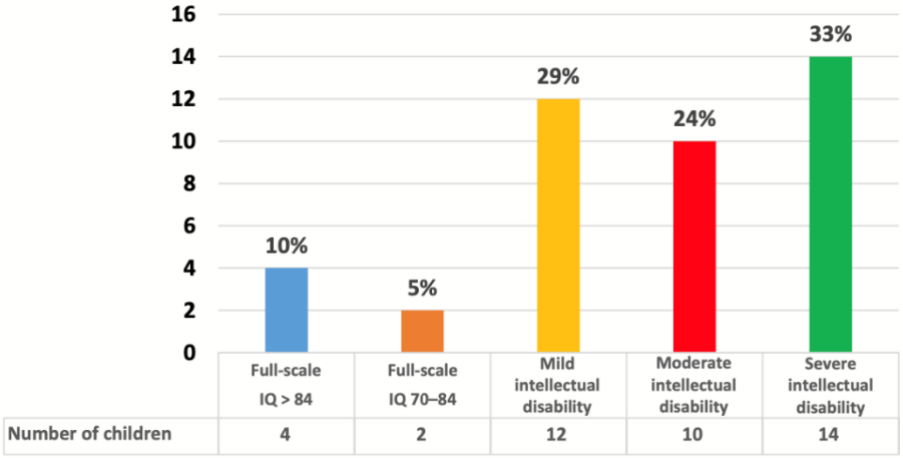

Figure 6. Intellectual function in 42 children with Dravet syndrome. From Paper III. Copyright 2022 Mac Keith Press. Reproduced with permission.

4.3.2 ADAPTIVE BEHAVIOUR

Thirty-nine (93%) children had a composite score on a measure of adaptive behaviour (VABS-II) ≥2 SD below the mean (i.e., ≥70), while 36 children

(86%) fulfilled diagnostic criteria for ID. This indicates that children with DS, who do not fulfil ID criteria, still can have significant problems with adaptive behaviour.

4.3.3 CHILDREN WHO DID NOT FULFIL A DIAGNOSIS OF INTELLECTUAL DISABILITY

There were six children who did not fulfil DSM- 5 criteria for ID. Two (4.8%) children had an IQ/DQ between 70 and 84, and four (10%) had normal intellectual function with an IQ between 87 and 108. These six children were between 5.2 and 16.7 years old. They had composite adaptive behaviour scores between 58 and 91 and only two children had adaptive behaviour scores ≥70. There was also one child with ID and a composite adaptive behaviour score ≥70.

All six children who did not have ID, fulfilled all criteria for DS used in our study[37] and all the ILAE criteria for DS from 2022 with the exception of not having ID[1]. All six had experienced convulsive seizures lasting more than 30 minutes and all had drug resistant epilepsy with ongoing focal to bilateral tonic clonic seizures. The first seizure occurred between the age of three and seven months. Five out of six children had a *SCN1A* variant that could explain DS. Five children had experienced a median of four different seizure types (range 3-5). Those five children had experienced myoclonic seizures and had experienced their first febrile seizure between the age of four and seven months. Occurrence of myoclonic and febrile seizures and number of different seizure types were unknown in one child. In conclusion, we found 6/42 (14%) children without ID, but otherwise with a typical DS phenotype. A DS diagnosis for these children likely leads to easier access to DS treatment algorithms, new ASM trials and to DS support organisations.

4.3.4 COGNITIVE STRENGTHS AND WEAKNESSES

In our study, results on the Wechsler scales showed a significant weakness regarding the Processing speed index in comparison with the Fluid index ($p<0.001$) and the Working Memory index ($p<0.001$), indicating relative difficulties with attention, processing speed, and fine motor skills. Problems with attention are common in DS according to caregivers[1, 8, 9]. Processing speed has also been identified as a relative weakness in the general paediatric population with epilepsy[146, 147].

Results on the Wechsler scales also showed a significant weakness regarding Verbal comprehension index in comparison with Visual spatial index (p=0.045), indicating a relative weakness in language. Results on different domains of VABS-II are presented in Table 7. Communication was a relative weakness with a lower mean score compared with the Daily living skills domain (p<0.001) on the VABS-II. Problems with verbal communication in DS are confirmed in other studies[107, 148]. Speech impairment was reported by caregivers in 80% of individuals with DS six years and older[107]. A specific speech profile has also been described in DS with impairment of oral motor planning, specific symptoms of dysarthria and impressive and expressive language impairment[148].

Table 7. Mean scores for adaptive behaviour on Vineland Adaptive Behavior Scales – Second Edition (VABS-II) domains in 42 children with Dravet syndrome as described in Paper III. The domains Daily Living Skills and Socialisation were relative strengths with significantly higher mean scores compared with Communication and Motor Skills. From Paper III. Copyright 2022 Mac Keith Press. Reproduced with permission.

	Communication	Daily living skills	Socialization	Motor skills	Adaptive behaviour composite
Normal, *n* (%)	4 (10)	10 (24)	3 (7)	1 (7)	3 (7)
>2 SD below mean, *n* (%)	38 (90)	32 (76)	39 (93)	13 (93)	39 (93)
Mean score	48.64	54.79	52.79	52.86	45.40
SD	16.24	16.57	12.62	12.01	17.20
Range	20–91	29–99	34–86	31–72	20–91

The VABS-II domain `Socialization´ was a relative strength compared with Communication (p=0.001) and Motor Skills (p=0.036) domains in our study.

This confirms results from an earlier study showing a behavioural profile with `Socialization´ as a relative strength and Communication as relative weaknesses in children with DS[149]. A specific profile in children with DS and concomitant ASD has been suggested with a relative preservation of social skills, possibly leading to an under-diagnosis of ASD[150].

The Motor skills domain was also a relative weakness with lower mean scores compared with the Daily living skills domain (p=0.004) on the VABS-II. In another study, motor delay was apparent before two years of age in 50% of children with DS, and there was an increase in delay with age, affecting balance, visual motor integration, strength, coordination and locomotion[151]. Gait abnormalities have been shown as early as at four years of age in DS in instrumented gait analysis[152].

4.3.5 FACTORS RELATED TO INTELLECTUAL DISABILITY AND ADAPTIVE BEHAVIOUR

Greater deficits both in intellectual function (p=0.013) and adaptive behaviour (p<0.001) were associated with increased autistic symptoms in our study. In other studies, children with DS and concomitant ASD have been shown to have more severe ID than children without ASD[150, 153].

Deficits in adaptive behaviour were associated with older age at examination (p=0.006), and no child less than five years of age fulfilled criteria for severe ID. Several previous studies have shown cognitive slowing in the pre-school years in DS, but in most children, there seem to be a positive cognitive development later, albeit with a slowing compared to the normal population[9, 37, 154].

Deficits in adaptive behaviour were also associated with younger age at first episode of SE (p=0.003), possibly indicating a more severe phenotype or a direct effect of SE on cognition. There was no significant association between deficits in adaptive behaviour and epilepsy severity.

4.3.6 CONCLUSION

- Most children with DS had ID, and 57% had moderate to severe ID. The high number of children with ID (with a majority with moderate to severe ID) is in line with previous studies.

- There were more children with an adaptive behaviour score ≥2 SD below the mean (n=39) than children who fulfilled diagnostic criteria for ID (n=36). This implies that children with DS who do not fulfil ID criteria still can have significant problems with adaptive behaviour (Paper III).

- Adaptive behaviour and Wechsler scales profiles indicated relative difficulties with attention, processing speed, motor skills, and verbal communication. These results confirm results from earlier studies.

- The domain `Socialization` was a relative strength in adaptive behaviour, confirming results from earlier studies. This relative strength might lead to an under-diagnosis of ASD in DS[150].

- Problems with intellectual function and adaptive behaviour both increased with increased autistic symptoms, confirming results from earlier studies.

4.4 BEHAVIOUR, SLEEP, AND QUALITY OF LIFE (PAPER IV)

In paper IV we found clinically significant behavioural and emotional problems in 29/40 (72%) children, clinically significant insomnia in 18/42 (43%) and `poor´ or `very poor´ QoL in 7/41 (17%) children. Behaviour could not be assessed in two children (one and two years old), and QoL in one child (one year old) due to young age.

4.4.1 BEHAVIOUR AND EMOTIONS

This is one of the first study using an instrument validated for children with moderate to severe/profound ID (the DBC) when evaluating behaviour and emotions in DS, increasing the possibility of capturing behaviours that are common in children with such levels of ID.

The median composite DBC score for the cohort was 54.5 (range (34-77), and 29/40 (72%) children had a composite DBC score>50 and thus scored in the range of 'serious' concern for behaviour. In another study, individuals with DS had significantly more behavioural problems compared with the general population and with individuals with *SCN1A* related disorders other than DS[10].

In the current study, 28 (70%) children scored in the serious range of concern for the Self-absorbed subscale of DBC, 25 (62%) for the Anxiety subscale, 24 (60%) for the Disruptive subscale, 24 (60%) for the Communication Disturbance subscale, and 18 (45%) for the Social Relating subscale.

The DBC subscale Social Relating had significantly less serious problems than all the other subscales; Disruptive ($p=0.003$), Communication disturbance ($p=0.002$), Anxiety ($p=0.003$) and Self-absorbed ($p<0.001$). The relative strength of the social relating subscale is in line with results of the VABS-II, presented in Paper III, showing that the domain `Socialization´ had significantly better scores than Communication and Motor skills domains. Children with DS, including those who fulfil ASD criteria, have shown better results on the domain `Socialization´, compared with other domains, as measured on the VABS scale, in another study[149]. However, these skills can mask severe problems with social understanding, and an underlying ASD diagnosis.

The linear regression showed a significant association between total behavioural problems and autistic symptoms, as measured with the SCQ, ($p=0.013$). This implies that increased autistic symptoms can explain some of the behavioural difficulties in DS. Consequently, strategies used to treat behavioural difficulties in children with ASD might also be effective in children with DS.

Behavioural problems, such as aggression, hyperactivity, anxiety and depressive behaviour have been present in 37-100% of individuals with DS, when measured with standardised instruments[9]. However, to our knowledge, earlier studies have seldom used instruments validated for use in children with moderate to severe ID when describing behaviour in children with DS, even though ca. 60% of children have this level of ID[9].

4.4.2 SLEEP

In our study, the number of participants with different degrees of insomnia according to the ISI scale was 4/42 (10%) with severe clinical insomnia, 14/42 (33%) with moderate clinical insomnia, 6/42 (14%) with subthreshold insomnia, and 18/42 (43%) with no clinical insomnia. These results are in line

with two other studies on individuals with DS, one with an abnormal sleep score in 44% of individuals[12] and another with sleep related problems in 42%[14].

Results for the ISI in our study, indicated that severe/very severe problems falling asleep (n=7/42, 17%) were less common than severe/very severe problems waking up at night (n=14/42, 33%), being disturbed in daily activities due to insomnia (n=15/42, 36%), or caregivers being dissatisfied with current sleep pattern (n=17/42, 40%). Difficulties falling asleep had previously been treated with Melatonin in 8/42 (19%) children, whilst 11/42 (26%) children were currently treated with this medication. Melatonin can decrease sleep latency and wakefulness after sleep onset in children with epilepsy[155], possibly reducing problems falling asleep among children in our study.

More severe ASM side effects according to the ELDQOL Side Effects subscale were associated with more severe insomnia according to composite ISI scores in a linear regression model in our study (p=0.032). There were no other factors associated with sleep difficulties in this model. According to a caregiver survey, ASMs negatively affected daytime drowsiness in half of children with DS[156]. ASMs, used in DS, might affect sleep-related problems in different ways. Clobazam in combination with cannabidiol, valproate, and higher dose levetiracetam have been shown to increase drowsiness during the day[157-159]. Clobazam has reduced sleep latency and improved sleep efficacy[160]. According to a review, benzodiazepines increased stage 2 non-REM sleep, which might lead to increased subjective sleep satisfaction with less awakenings, but also to reduced slow wave sleep and REM sleep[161]. Reduction in REM sleep and slow wave sleep may affect concentration and working memory negatively according to this review.

4.4.3 QUALITY OF LIFE

Caregivers answered one global question of QoL from ELDQOL in our study. The QoL of the child was considered `poor´ or `very poor´ in 7/41 (17%), `reasonable´ in 12/41 (29%) and `good´ or `very good´ in 22/41 (54%) children.

In another study, caregivers of children with refractory epilepsy answered a similar single global question evaluating QoL as in our study[131]. In this study only 2.5% of caregivers answered that the QoL of their child was `poor´. `Very

poor´ was not an alternative. Thus, more children with DS might have poor QoL compared with other children with refractory epilepsy. A study by Brunklaus and co-workers indicated that children with DS have, as a group, lower HRQoL compared with children with epilepsy with and without learning difficulties and compared with normative data[8].

In the current study, more severe insomnia according to the ISI scale was associated with reduced QoL (p=0.016). In children with epilepsy, sleep-related problems have been significantly associated with reduced HRQoL[162], but this association has not previously been described in DS.

4.4.4 CONCLUSION

- This is one of the first population-based studies that comprehensively describe behavioural difficulties in DS.

- It is also one of the first studies using an instrument validated for children with moderate to profound ID to investigate behaviour in children with DS.

- Significant behavioural problems were reported in 29/40 (72%) children, in line with previous research.

- Significant sleep difficulties were found in 18/42 (43%), also in line with previous research.

- According to caregivers 7/41(17%) children had `poor´ or `very poor´ QoL in our study.

- More behavioural problems were correlated to increased level of autistic symptoms, indicating that some behavioural problems might be explained by autistic symptoms. Thus, treatments used for behavioural difficulties in ASD might be effective also in DS.

- More severe insomnia was associated with reduced QoL. This association has been shown in children with other epilepsies but has not been described in DS before.

5 STRENGTHS AND LIMITATIONS

This is, to our knowledge, one of the first population-based studies that comprehensively describes epilepsy and psychosocial aspects of DS. Major strengths of the study are the population-based design and the systematic investigation that was performed to identify all children with a DS diagnosis in Sweden. The participation in all parts of our study was more than 80%. This reduces the risk for selection bias, which might be a problem in other studies[163]. Other strengths are that the DS diagnoses have clinically been confirmed by two experienced paediatric epileptologists and all caregivers have been interviewed and their children have been examined by one of these two epileptologists.

A specific strength of Paper III is that adaptive behaviour has been assessed and used to evaluate the level of intellectual functioning, in line with current DSM-5 criteria[63]. Validated psychological instruments have been used to evaluate intellectual function and adaptive behaviour, and one experienced psychologist (CR) has undertaken all psychological assessments. A specific strength in Paper IV is that we used an instrument validated for children with moderate to profound ID (the DBC) when evaluating behaviour. Such instruments have, to our knowledge, not been used before in DS. Instruments adapted to different levels of ID, are important for capturing behaviours typically for children with moderate to profound ID.

Adjustments for multiple tests (e.g., Bonferroni adjustments)[164] have been used in some studies to reduce the risk for type 1 errors by gradually reducing the p-value that is deemed significant depending on the number of analyses performed. A type 1 error means that non-significant differences are deemed significant and that the null hypothesis is falsely rejected. We chose not to use the Bonferroni adjustments, since they also increase the risk for false negative type 2 errors, so that important differences are judged to be non-significant[165]. To avoid type 2 errors is of special importance in this study as little is known regarding correlations between epilepsy, cognition, behaviour, sleep, QoL, seizure-provoking factors and other factors in DS. Thus, the associations found in this study, need to be confirmed in larger studies.

There are some limitations that need to be borne in mind in interpreting the results. The number of participants in our study is relatively small, compared to larger studies[8, 163, 166-168]. This reduces the power of the study, making it more vulnerable, especially for type 2 errors. As the number of participants is relatively small, the results of statistical analysis should be interpreted with caution.

Another weakness of the study, that could affect both the incidence and the mortality rate of children with DS in our study, is that we did not perform screening of all young children with recurrent febrile or afebrile seizures as in some other studies[169, 170]. In addition, there are no Swedish comprehensive local or national epilepsy registries. Consequently, there might be children with a DS diagnosis, alive or deceased, that were unknown to us. However, all children with drug-resistant epilepsy in Sweden are followed by a paediatric neurologist, and there is a low threshold to refer children with difficult to treat epilepsy to a university hospital, with expertise in epilepsy and knowledge of DS.

In Papers I-II we did not include a control-group of children with other types of epilepsy. An additional limitation is that the interview was bespoke and has not been validated. However, the use of a semi-structured face-to-face interview with caregivers in these two papers, allowed the opportunity to probe for clarification and increase understanding of responses. The study was cross-sectional and data on ASMs, seizure types, seizure provoking factors, and strategies to control seizures, were collected retrospectively and might be affected by recall bias. Another weakness is that we did not use video-EEG to confirm seizure types reported by caregivers and we did not use seizure diaries specified for this study. Seizure provoking factors might be influenced by the subjectivity of the caregiver and the caregiver could oversimplify the explanation of the seizure[171], thus self-reported information on seizure precipitants should be interpreted with caution[171].

In Paper III a specific weakness is that intellectual functioning could not be measured with the same method in all children. Another weakness is that it was not possible to use linear regression with respect to cognitive scores. This could have impacted results of the regression analysis. Thus, results of statistical analyses should be interpreted with caution. The Griffiths Mental

Development Scales was used to assess many children who were outside the age range of this test.

A specific weakness in Paper IV is that the ISI, used to measure insomnia, is not validated for use in children, and might not identify some sleep difficulties (e.g., needing caregivers in the room to fall asleep and moving to someone else's bed during the night) seen in children. At the time of the study, there were no instruments measuring sleep validated for children available in Swedish. However, the ISI has been used as a proxy instrument, answered by caregivers, to measure sleep related problems in children with cerebral palsy[125]. A Cronbach's alpha=0.90 for the ISI subscales in the current study, indicates an adequate internal consistency.

QoL was measured by one single global question (Paper IV), that does not cover subcomponents of QoL[104]. However, this approach has been successfully employed previously[172]. In one study, a single global QoL question was able to detect clinically important changes in QoL and showed moderate to good correlation when compared with two comprehensive HRQoL scales[131].

6 CONCLUSIONS

- This is one of the first population-based studies that comprehensively describes epilepsy and psychosocial aspects of DS.

- Cumulative incidence was higher, age at DS diagnosis lower and less children had used contra-indicated sodium-channel blockers in the `younger´ age group indicating an increased awareness of DS (Paper I).

- In our study 96% had a *SCN1A* variant that could explain DS. The proportion of *SCN1A* positive individuals with DS seems to gradually have increased over time, indicating better genetic assessments (Paper I).

- Tonic seizures were described in 25/42 (60%). This is higher than in previous studies[140, 141] (Paper I).

- In this study we present a range of different seizure provoking factors, described by caregivers. The most common were internal and external changes in temperature, strong emotions, and infections without fever. To our knowledge there is only one previous Dutch study[7], comprehensively describing, caregiver reported seizure precipitants in DS (Paper II).

- Seizures had been provoked by at least two factors in all children, according to caregivers. This is in line with the results in a Dutch study[7]. Measures to prevent seizures had been used for all children. To our knowledge, such measures have not comprehensively been described before in DS (Paper II).

- Seizures provoked by reduced ambient temperature were reported in almost 50% of children. This has to our knowledge not been described before (Paper II).

- Most children with DS had ID, and 57% had moderate to severe ID. The high number of children with ID (the majority with moderate to severe ID) is in line with previous studies[9] (Paper III).

- There were more children with an adaptive behaviour score ≥2 SD below the mean (n=39) than children who fulfilled diagnostic criteria for ID (n=36). This

implies that children with DS who do not fulfil ID criteria still can have significant problems with adaptive behaviour (Paper III).

- The domain `Socialization` was a relative strength in adaptive behaviour, confirming results from earlier studies. This relative strength might lead to an under-diagnosis of ASD in DS (Paper III).

- Significant behavioural problems were found in 72% and significant sleep difficulties in 43%. These results are in line with other studies (Paper IV).

- More behavioural problems were associated with increased level of autistic symptoms, indicating that some behavioural problems might be explained by autistic symptoms. Thus, treatments used for behavioural difficulties in ASD might be effective also in DS (Paper IV).

- More severe insomnia was associated with reduced QoL. This association has been shown in children with epilepsy but not in DS (Paper IV).

- In this doctoral thesis we comprehensively describe factors that could affect the burden of illness and QoL in DS, such as the high number of reported seizure provoking factors and means to avoid seizures, the high proportion of ID and sleep-related, behavioural, and emotional problems.

7 CLINICAL IMPLICATIONS

There is a need to regularly re-evaluate aetiology in children and adults with drug-resistant epilepsies where the cause of the epilepsy is unknown. This is important in order to identify individuals with diagnoses, such as DS, where precision therapies, such as avoiding sodium-channel blockers, can improve prognosis[173-175]. A new genetic investigation in such patients is often an essential part of the re-evaluation, as these procedures have become more accurate with time[138].

Seizure provoking factors and measures taken to avoid seizures should be actively asked for in all children with DS, as such factors and measures appears to be common in DS, and as they might affect seizure outcome and QoL.

There is a need for a formal evaluation of cognition, adaptive behaviour, and behavioural problems in children with DS. Assessment for neurodevelopmental difficulties such as ID and ASD should be undertaken in the preschool years to ensure that the child is offered optimal understanding and support.

There is a need to evaluate possible coexisting sleep difficulties in DS as these can adversely impact behaviour and QoL.

It is important to regularly ask for and evaluate psychosocial issues in all children with DS, as such problems can affect QoL for the child and the whole family.

8 FUTURE PERSPECTIVES

There is a need for increased genetic testing in drug-resistant epilepsies, including genetic screening of DS and other DEEs. New disease specific treatments with precision-medicine and gene-therapy may improve outcome and mortality.

There is a need for further large studies on outcome, mortality and SUDEP. Previous larger studies on mortality ended in 2009, 2010 and 2015[4, 47, 48]. New disease specific treatments and more diagnosis specific treatment algorithms may have changed outcome and even mortality. Recent studies on Fenfluramine in DS have for example indicated good seizure-reducing effects, improvement of executive functioning[176] and reduced SUDEP-rate[177].

In addition to genetic diagnosis, seizure type is important for the choice of treatment. Monitoring seizures in a more comprehensive way with video EEG will help to distinguishing the different seizure types in DS. This could confirm our finding, indicating that tonic seizures are more common than earlier described in DS.

Seizures in DS respond only partly to ASMs. In our study seizure provoking factors were commonly experienced and avoided by caregivers. This seems to be an important part of treatment strategy. Identification and interventional studies to confirm seizure provoking factors could probably enhance the knowledge of caregivers and healthcare providers and improve seizure burden and QoL.

In our study, caregivers of children with DS used many different non-pharmacological measures to avoid seizures. Some measures might diminish seizure burden, leading to better safety and QoL, but some measures may adversely affect family functioning and further burden the psychosocial impact of caring of a child with DS. Studies investigating the efficacy of such measures are needed.

Some measures to avoid seizures in DS like use of air conditioning, which otherwise is unusual in Sweden, and use of seizure alarms and home oxygen in prolonged seizures might lead to an increased economic burden for the family and/or the society, underlining the importance to evaluate the

effectiveness of such devices. There are indications that sharing a bedroom reduces the SUDEP risk[45], but the evidence that seizure alarms protect against SUDEP is weaker, and there is a need to investigate the effectiveness of such devices.

Regarding cognition and behaviour there is a need for multicentre studies, if possible, population-based, with a greater number of participants than in the current study. These studies can help evaluate possible cognitive and behavioural profiles and confirm associations found in this study. There is also a need to further evaluate interventions that affect behaviour and sleep in DS and their effect on QoL.

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