Caregiver reported seizure precipitants and measures to prevent seizures in children with Dravet syndrome

Björn Bjurulf a,b,c, *, Colin Reilly a,b,c, Tove Hallböök a,b,c

a Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg 405 30, Sweden
b Queen Silvia Children’s Hospital, Sahlgrenska University Hospital, Gothenburg 416 85, Sweden
c Member of the ERN, EpiCARE, Gothenburg, Sweden

ARTICLE INFO

Keywords:
Child
Dravet syndrome
Epilepsy
Prevention
Precipitants

ABSTRACT

Objective: The aim of this population-based, cross-sectional study was to describe caregiver-reported seizure precipitants, measures taken to prevent seizures and rescue therapies in children with Dravet Syndrome (DS).

Method: In a population-based study, caregivers of 42/48 Swedish children with DS born between 2000 and 2018 were interviewed. Frequency of precipitants, preventive measures, and rescue therapies were compared between children born 2000-2009 and 2010-2018 and between ‘severe’ and ‘less severe’ epilepsy.

Results: All children had experienced precipitants. Preventive measures were employed in all. Seizures had been provoked by a median of seven (range 2-11) out of 13 factors. A median of eight (range 1-17) preventive measures out of 19 were reported. The most common precipitants were fever (n=42, 100%), and afebrile infections (n=39/42, 93%). Afebrile infections (p=0.014) and reduced ambient temperature (p=0.006) were more common precipitants in younger children, and bright light in children with severe epilepsy (p=0.013). The most common factors avoided were warm weather (n=35/42, 83%) and physical activity (n=27/42, 64%). It was more common to avoid strong emotions (p=0.035) and reduced temperature (p=0.002) in younger children, and to avoid infections (p=0.024) and crowds (p=0.046) in children with ‘severe’ epilepsy. Many children (n=28/42, 67%) or their siblings (n=27/42, 64%) or their siblings (n=20/42, 47%) had stayed home to avoid infections in school/day-care. Use of emergency medicines was more frequent in younger children (p=0.006) and in children with ‘severe’ epilepsy (p=0.007).

Significance: Caregiver-reported seizure precipitants are common in DS. Caregivers employ a range of measures to avoid seizures, restricting family life.

1. Introduction

Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy1, characterized by multiple intractable seizure types and frequent episodes of status epilepticus (SE). Seizures usually start in the first year of life2. DS is usually caused by dominant pathogenic variants in the Sodium voltage-gated channel alpha subunit 1 (SCN1A) gene3. Most affected individuals meet the criteria for intellectual disability and behavioral problems are common4. The incidence has been calculated to 1 per 15,500 live births in a prospective study5. Previous studies have identified several possible seizure precipitants in individuals with DS6. In a Japanese study, seizures in DS could be provoked by increasing the body temperature to 38 degrees by immersion in a hot bath7. Seizures in DS can also be provoked by hyperthermia due to immunization or febrile infections8-9. However, few studies have systematically investigated different seizure precipitants6,10. There was a strong consensus in a North American consensus panel, that allowing the child to nap if tired and avoidance of overexertion and high ambient temperature could reduce seizures in at least a modest number of patients with DS11. Avoidance of flashing lights and of placing the patient in a bath as well as use of cooling vests and sunglasses were considered effective measures to prevent seizures in a minority of patients by the

Abbreviations: Dravet Syndrome; DS; Epilepsy and Learning Disabilities Quality of Life scale, ELDOQ; scale; Health related Quality of Life, HRQoL; National Institute for Health and Care Excellence, NICE; Status Epilepticus, SE; Sodium voltage-gated channel alpha subunit 1, SCN1A; Sudden Unexpected Death in Epilepsy, SUDEP.

* Corresponding author at: Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg 405 30, Sweden.

E-mail address: bjorn.bjurulf@vgregion.se (B. Bjurulf).

https://doi.org/10.1016/j.seizure.2022.09.018
Received 1 July 2022; Received in revised form 19 August 2022; Accepted 25 September 2022
Available online 30 September 2022
1059-1311 © 2022 The Author(s). Published by Elsevier Ltd on behalf of British Epilepsy Association. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
panel. Otherwise, there is very limited research on measures employed by caregivers of children with DS to avoid seizures and on the effectiveness of such measures. Repetitive episodes of SE are very common in DS, and a major goal is fast and effective treatment of seizures. In one study of children with DS, 90% had used emergency seizure medications in the last three months.

Previous research suggests that health related quality of life (HRQoL) in DS is reduced compared to children with other epilepsy syndromes. Achieving better seizure control is a key aspect in improving HRQoL of individuals with epilepsy, and reduced seizure control is an independent risk factor for decreased HRQoL in DS. We conducted a population-based study of DS and have reported on epilepsy and its treatments. In the current study we investigate seizure precipitants, and caregivers’ measures to avoid seizures and use of rescue therapy in Swedish children with DS.

2. Material and methods

This is a population-based, cross-sectional study of 42/48 Swedish children with known DS as of December 31, 2018, whose caregivers consented to participate in clinical assessment. We have previously reported on epilepsy and its treatment in these 42 children. Inclusion criteria are those reported by Nabbout et al.: (a) a normal EEG and no preexisting cerebral lesion in a normal infant; (b) normal development until the first seizure occurring before one year of age; (c) refractory clonic or tonic-clonic seizures affecting one or both sides simultaneously or alternatively; (d) exclusion of any other identified epilepsy syndrome including negative PCDH19 analysis in SCN1A negative participants. All but two children had a SCN1A variant and 19/42 (45%) were females. Clinical characteristics are presented in Table 1. Questions on seizure precipitants, measures used by caregivers to avoid seizures and use of rescue therapy were asked in a face-to-face interview (Supplement 1). The questions were based on clinical experience and earlier studies. Interviews were conducted between October 15th 2018 and April 3rd, 2020.

2.1. Analysis

Epilepsy severity, defined as ‘severe/less severe’ epilepsy, was investigated based on five items from the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) scale, previously employed in a study of DS by Brunklaus et al. The items were: 1 = How severe have your child’s seizures been in the last 4 weeks? 2 = In the last 4 weeks how well do you think your child’s seizures have been controlled by the drugs he/she is taking? 3 = How often in the last 4 weeks has your child been prevented from taking part in his/her normal activities by his/her seizures/epilepsy? 4 = How concerned have you been about your child because of his/her epilepsy? 5 = How severe a condition do you think the epilepsy is? The overall epilepsy severity was calculated as the average response to all five items and was classified as ’severe/less severe’ based on a median split. The ELDQoL scale could not be used in one child due to low age. Thus, data on epilepsy severity was available in 41/42 children.

To compare frequency of different precipitants and measures to avoid seizures in children with ‘severe/less severe’ epilepsy and children in the younger (born 2010-2018) and older (born 2000-2009) age-group a Chi square test was used if expected count in all categories were ≥5. Otherwise, a Fisher’s exact test was used. A Mann Whitney U test was used to compare number of seizure precipitants and frequency of rescue medication used the last three months, between older and younger children, and between children with ‘severe/less severe’ epilepsy. Missing data for each specific precipitant/measure were not included in the analyses. P-value < 0.05 was considered statistically significant in all the analyses. The PASW Statistics for Windows, ver.28 software (IBM Corporation, Armonk, NY, USA) was used for the statistical analyses.

### Table 1

Clinical characteristics of 42 Swedish children with Dravet syndrome (DS) born 2000–2018.

| Variable                                                      | n (%)  |
|---------------------------------------------------------------|--------|
| Age at assessment (y), median (range)                        | 8.8 (1.1–19) |
| Age at DS diagnosis (y), median (range)                      | 2.4 (0.53–10) |
| Sex                                                          |        |
| Females                                                       | 19 (45) |
| Males                                                        | 23 (55) |
| Pathogenic or likely pathogenic SCN1A variant                |        |
| No SCN1A variant                                             | 2 (4.8) |
| Known SCN1A variant                                          | 40 (95) |
| De novo variant                                               | 36 (86) |
| Inherited from parents                                       | 4 (9.5) |
| Epilepsy                                                      |        |
| Age at first seizure (y), median (range)                     | 0.42 (0.13–2.3) |
| Age at epilepsy diagnosis (y), median (range)                | 0.81 (0.33–4.5) |
| Epilepsy severity score¹                                    | 3 (1–4) |
| Current and/or previous seizure types                        |        |
| Focal or focal to bilateral tonic clonic                      | 42 (100) |
| Myoclonic                                                    | 35 (83) |
| Atypical absences                                            | 35 (83) |
| Tonic                                                        | 25 (60) |
| Atonic                                                       | 15 (36) |
| Neurodevelopment                                              |        |
| Intellectual disability                                      | 28 (65) |
| Autism spectrum disorder                                     | 19 (44) |
| Attention deficit hyperactivity disorder                     | 4 (10) |
| Neurological deficit                                          |        |
| Ataxia                                                       | 26 (62) |
| Crouch gait                                                  | 17 (40) |
| Mild hemiparesis                                             | 2 (4.8) |
| ASMs                                                         |        |
| Number of current ASMs, median (range)                      | 6 (1–20) |
| Total number of ASMs, median (range)                        | 13 (5–20) |
| Types of ASMs currently and/or previously used              |        |
| Valproate                                                    | 42 (100) |
| Benzodiazepines                                              | 40 (95) |
| Levetiracetam                                                | 35 (83) |
| Stiripentol                                                  | 26 (62) |
| Sodium-channel inhibitors                                    | 24 (57) |
| Topiramate                                                   | 24 (57) |
| Phenobarbital                                                | 13 (31) |
| Zonisamide                                                   | 8 (19)  |
| Cannabidiol                                                  | 3 (7.1) |
| Other ASMs                                                   | 10 (24) |

Out of 42 identified children with DS, 41 were born in Sweden. Data in the table has been published previously.

ASMs, Anti-seizure medications; SCN1A, gene encoding the sodium voltage-gated channel type 1 alpha subunit.

¹ Unless stated as median (range) for the variable.

² Epilepsy severity was investigated based on five items from the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) scale.

Based on clinical assessment by pediatric neurologist Björn Bjurulf or Tove Hallböök.

Mild hemiparesis in one patient due to a benign infratentorial cerebral tumor and in another patient after a prolonged episode of convulsive status epilepticus.

Carbamazepine, Lacosamide, Lamotrigine, Oxcarbazepine, Phenytoin or Rufinamide.

Acetazolamide, Ethosuximide, Perampanel, Prednisolone, Sulthiame or Vigabatrine.

3. Results

3.1. Seizure precipitants

Seizure precipitants are described in Table 2. Of 13 possible seizure precipitants seizures were currently provoked by a median of seven
### Table 2
Seizure precipitants according to caregivers.

| Factor                        | All children n (%) * | Older children n (%) * | Younger children n (%) * | Chi square | p     | 'Severe' epilepsy n (%) * | 'Less severe' epilepsy n (%) * | Chi square | p     |
|-------------------------------|----------------------|------------------------|--------------------------|------------|------|--------------------------|-----------------------------|------------|------|
|                               | Yes, now             | Earlier                | No                       | Unknown    | Yes now | Yes now                    | Yes now                     | Yes now    |       |
| Infection with fever          | 37/88 (42)           | 5 (12)                 | 0                        | 0          | 14/18 (78) | 23/24 (96)                | na                          | 0.15<sup>4<sup>  | 0.99<sup>4<sup>   |
| Afebrile infections           | 28/67 (42)           | 11 (26)                | 2                        | 1 (2.4)    | 8/17 (47)  | 20/24 (83)                | 6.0                         | 0.014<sup>6<sup> | 0.99<sup>6<sup>   |
| Physical activity             | 27/64 (42)           | 8 (19)                 | 6                        | 1 (2.4)    | 10/18 (56) | 17/23 (74)                | 1.5                         | 0.22<sup>5<sup>  | 0.99<sup>5<sup>   |
| Tiredness                     | 29/69 (42)           | 3 (7.1)                | 8                        | 2 (4.8)    | 13/17 (76)| 16/23 (70)                | 0.73<sup>6<sup>  | 0.99<sup>6<sup>   |
| Warm weather                  | 26/62 (42)           | 3 (7.1)                | 11                       | 2 (4.8)    | 12/18 (67) | 14/22 (64)                | 0.04                         | 0.84<sup>5<sup>  | 0.99<sup>5<sup>   |
| Strong emotions               | 25/60 (42)           | 2 (4.8)                | 15                       | 0          | 8/18 (44)  | 17/24 (71)                | 3.0                         | 0.08<sup>2<sup>  | 0.99<sup>2<sup>   |
| Sleep                         | 23/55 (42)           | 2 (4.8)                | 16                       | 1 (2.4)    | 10/17 (59) | 13/24 (54)                | 0.09                         | 0.77<sup>4<sup>  | 0.99<sup>4<sup>   |
| Crowds                        | 19/45 (42)           | 3 (7.1)                | 16                       | 4 (9.5)    | 6/17 (35)  | 13/21 (62)                | 2.7                         | 0.10<sup>2<sup>  | 0.99<sup>2<sup>   |
| Reduced ambient temperature   | 18/43 (42)           | 2 (4.8)                | 20                       | 2 (4.8)    | 3/16 (19)  | 15/24 (62)                | 7.4                         | 0.006<sup>6<sup> | 0.99<sup>6<sup>   |
| Bright light                  | 16/38 (42)           | 3 (7.1)                | 20                       | 3 (7.1)    | 7/17 (41)  | 9/22 (41)                 | <.001                        | 0.99<sup>2<sup>  | 0.99<sup>2<sup>   |
| Noise                         | 10/24 (42)           | 1 (2.4)                | 31                       | 0          | 4/18 (22)  | 6/24 (25)                 | na                          | >0.99<sup>4<sup> | 0.99<sup>4<sup>   |
| Geometric patterns            | 9/21 (42)            | 1 (2.4)                | 32                       | 0          | 4/18 (22)  | 5/24 (21)                 | na                          | >0.99<sup>4<sup> | 0.99<sup>4<sup>   |
| Other factors                 | 8/19 (42)            | 2 (4.8)                | 29                       | 3 (7.1)    | 4/16 (25)  | 4/23 (17)                 | na                          | 0.69<sup>2<sup>  | 0.99<sup>2<sup>   |
| Number of factors             | 7/13 (9-11)          | 2 (4.8)                | 29                       | 3 (7.1)    | 4/16 (25)  | 4/23 (17)                 | na                          | 0.69<sup>2<sup>  | 0.99<sup>2<sup>   |
| number median (range)         |                      |                       |                          |            | 6.5 (0-10) | 7.0 (1-11)                | na                          | 0.16<sup>4<sup>  | 0.99<sup>4<sup>   |
| Number of factors at any time, median (range) | 7/13 (2-11) | 2 (4.8)                | 29                       | 3 (7.1)    | 7.0 (2-11) | 7.5 (3-11)                | na                          | 0.56<sup>4<sup>  | 0.99<sup>4<sup>   |

* Unless stated as median (range) for the variable.
* Children born 2000-2009, n=18.
* Children born 2010-2018, n=24.
* Chi square test with 1 degree of freedom (used for tests with all expected values >5).
* Epilepsy severity, defined as ‘severe/less severe’ epilepsy, was investigated based on five items from the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) scale<sup>18</sup> and was classified as ‘severe/less severe’ based on a median split. Data on epilepsy severity was available in 41/42 children.
* Fishers exact test (used for tests with at least one expected value <5).
* n=42.
* n=41.
* n=40.
* n=39.
* n=38.
* n=37.
* One to three factors in each child: constipation n=4, change in weather n=2, food not given at usual time n=1, tactile stimulation n=1, pain n=1, catamenial n=1, transition between awaked state and sleep n=1, change between darkness and light n=1.
* Mann Whitney U test.

All 42 children had experienced infections with fever and all but three (93%) infections without fever as seizure precipitants. Other common current or previous seizure precipitants were physical activity (n=35/42, 83%), tiredness (n=32/42, 76%) and warm weather (n=29/42, 69%). Seizure precipitants, not specifically asked for in the questionnaire were mentioned spontaneously in 10/42 (24%). Of those, constipation was most common and described in four (9.5%) children.

Afebrile infections were a current triggering factor in 20/24 (83%) younger and 8/17 (47%) older children, X²(1, n=41)=6.0, p=0.014. Reduced ambient temperature was a current triggering factor in 15/24 (62%) younger and 3/16 (19%) older children, X²(1, n=40)=7.4, p=0.006. Bright light was a seizure precipitants in 12/20 (60%) children with ‘severe’ epilepsy, and 4/19 (21%) children with ‘less severe’ epilepsy; X²(1, n=39)=6.1, p=0.013.

### 3.2. Caregiver-reported measures to avoid seizures

Caregiver reported measures to avoid seizures are described in Table 3. A median of eight (range 0-17) measures out of 19 asked for were currently used and a median of eight (range 1-17) had been used at any time. Warm weather was or had been avoided by 35/42 (83%) individuals, physical activity by 27/42 (64%) and infections and tiredness by 25/42 (60%) each. Methods employed to avoid infections were increased hand-hygiene in 24/42 (57%) children and avoiding contact with individuals with infections in 13/42 (31%). Twenty-eight (67%) children had stayed home from school to avoid infections such as...
Table 3
Measures to prevent seizures according to caregivers.

| Measures                                         | All children n (%) | Older children n (%) | Younger children n (%) | Chi square | p     | 'Severe' epilepsy n (%) | 'Less severe' epilepsy n (%) | Chi square | p     |
|-------------------------------------------------|--------------------|----------------------|------------------------|-----------|-------|------------------------|-------------------------------|-----------|-------|
| Avoid warm weather                              | Yes, n = 33 (79)    | 2 (4.8)              | 7 (17)                 | 0         | 14/18 (78) | 19/24 (79) | na                     | >0.99<br/> | 18/20 (90) | 14/21 (67) | na       | 0.13<br/> |
|                                                | Earlier n = 25 (40) | 15                   | 0                      | 9/18 (50) | 16/24 (67) | 1.2        | 20/20 (60) | 13/21 (62) | 0.016    | 0.90<br/> |
| Avoid physical activity                         | No                 | Unknown              | Yes, n = 23 (55)       | 1 (2.4)   | 8/18 (44) | 15/23 (65) | 1.8        | 0.18<br/> | 14/19 (74) | 8/21 (38)  | 5.1      | 0.024<br/> |
| Avoid infections                               | 2 (4.8)            | 36                   | Yes, n = 22 (55)       | 2 (4.8)   | 12/18 (67) | 11/22 (50) | 1.1        | 0.29<br/> | 11/19 (58) | 12/21 (57) | 0.002    | 0.96<br/> |
| Avoid tiredness                                 | 2 (4.8)            | 36                   | Yes, n = 21 (50)       | 3 (7.1)   | 7/18 (39) | 14/21 (67) | 3.0        | 0.08<br/> | 12/17 (71) | 8/21 (38)  | 4.0      | 0.046<br/> |
| Avoid crowds                                    | 2 (4.8)            | 16                   | Yes, n = 19 (50)       | 21 (50)   | 5/18 (28) | 14/23 (61) | 4.4        | 0.035<br/> | 12/20 (60) | 7/21 (33)  | 2.9      | 0.087<br/> |
| Avoid strong emotions                           | 1 (2.4)            | 21                   | Yes, n = 19 (50)       | 1 (2.4)   | 9/18 (50) | 8/24 (33)  | 1.2        | 0.28<br/> | 10/20 (50) | 6/21 (29)  | 2.0      | 0.16<br/> |
| Avoid bright light                              | 1 (2.4)            | 24                   | Yes, n = 15 (36)       | 3 (7.1)   | 3/18 (17) | 3/24 (12)  | na         | >0.99<br/> | 4/20 (20)  | 2/21 (9.5) | na      | 0.41<br/> |
| Avoid red temperature                           | 0                  | 25                   | Yes, n = 9 (21)        | 0         | 5/18 (28) | 4/24 (17)  | na         | 0.46<br/> | 5/20 (25)  | 3/21 (14)  | na      | 0.45<br/> |
| Avoid noise                                     | 6 (14)             | 3                   | Yes, n = 2 (4.8)       | 37 (88)   | 2 (7.1)   | 2/17 (12)  | 0/22       | 0.18<br/> | 1/19 (5.3) | 1/19 (5.3) | na      | >0.99<br/> |
| Avoid other factors                             | 2 (4.8)            | 0                   | Yes, n = 11/14 (52)    | 3 (7.1)   | 17/21 (41) | 15/22 (68) | 2.8        | 0.09<br/> | 16/19 (84) | 6/20 (30)  | 12      | <.001<br/> |
| Stays home if infection in school/ day care     | 11/34 (32)         | 5/34                 | Yes, n = 13/17 (34)    | 1/34 (2.9) | 2/13 (15) | 9/20 (45)  | na         | 0.13<br/> | 5/13 (38)  | 5/19 (26)  | na      | 0.70<br/> |
| Sibling stays home if infection in school/ day care | 24/57 (45)     | 2 (4.8)              | Yes, n = 16 (38)       | 1 (2.4)   | 9/18 (50) | 15/23 (65) | 1.0        | 0.33<br/> | 15/19 (79) | 8/21 (38)  | 6.8      | 0.009<br/> |
| Avoid infections-family members<sup>a</sup>     | 16/43 (38)         | 1 (2.4)              | Yes, n = 18 (43)       | 3 (7.1)   | 5/18 (28) | 11/21 (52) | 2.4        | 0.12<br/> | 9/18 (50)  | 6/20 (30)  | 1.6      | 0.21<br/> |
| Avoid infections-others<sup>a</sup>             | 17/40 (43)         | 2 (4.8)              | Yes, n = 17 (40)       | 2 (4.8)   | 5/18 (28) | 10/24 (42) | 0.32       | 0.86<br/> | 9/20 (45)  | 9/21 (43)  | 0.019    | 0.89<br/> |
| Air condition used                              | 17/40 (43)         | 2 (4.8)              | Yes, n = 22 (52)       | 0         | 5/18 (28) | 12/24 (50) | 2.1        | 0.15<br/> | 9/20 (45)  | 8/21 (38)  | 0.20    | 0.65<br/> |
| Use of any personal cooling device              | 22/52 (43)         | 0                   | Yes, n = 02/17 (55)    | 15        | 5 (12)   | 7/17 (41)  | 15/20 (75) | 4.4        | 0.037<br/> | 13/17 (76) | 9/19 (47)  | 3.2      | 0.07<br/> |
| Any prophylaxis against infections              | 7/17 (43)          | 3 (7.1)              | Yes, n = 3/17 (32)     | 0         | 0/18 (0)  | 7/24 (29)  | na         | 0.04<br/> | 4/20 (20)  | 3/21 (14)  | na      | 0.70<br/> |
| Antibiotic prophylaxis<sup>b</sup>              | 3 (7.1)            | 5 (12)               | Yes, n = 34 (81)       | 0         | 0/18 (0)  | 3/24 (12)  | na         | 0.25<br/> | 2/20 (10)  | 1/21 (4.8) | na      | 0.61<br/> |
| IVIG prophylaxis<sup>c</sup>                    | 4 (9.5)            | 0                   | Yes, n = 0/19 (0-17)   | na        | 6 (0-14)  | 10 (1-17)  | na         | 0.12<br/> | 10 (2-17)  | 6 (0-14)  | na      | 0.031<br/> |
| Preventive measures now, median (range)<sup>d</sup> | 8/19 (0-17)     | na                   | Yes, n = 8/19 (1-17)   | 7 (2-17)  | 10 (1-17) | na         | 0.18      | 11 (2-17)  | 7 (1-17)  | na      | 0.089<br/> |

<sup>a</sup> Unless stated as median (range) for the variable.
<sup>b</sup> IVIG intravenous immunoglobulin
<sup>c</sup> Children born 2000-2009, n=18.
<sup>d</sup> Children born 2010-2018, n=24.
<sup>e</sup> Chi square was used for tests with all expected values >5.
<sup>f</sup> Epilepsy severity, defined as ‘severe/less severe’ epilepsy, was investigated based on five items from the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) scale<sup>5,6</sup>, and was classified as ‘severe/less severe’ based on a median split. Data on epilepsy severity was available in 41 children.
<sup>g</sup> Fisher's exact test was used for all tests with at least one expected value < 5.
<sup>h</sup> n=42.
<sup>i</sup> n=41.
<sup>j</sup> Measures to avoid infections were performed. Caregivers were asked to describe how this was done.
<sup>k</sup> Increased hand hygiene (n=22), avoids individuals with infections (n=13), change clothes several times daily (n=1), shower after school (n=1)
<sup>l</sup> Increased hand hygiene (n=2), avoided contact with other children (n=1).
<sup>m</sup> n=40.
<sup>n</sup> n=39.
<sup>o</sup> n=38.
<sup>p</sup> In eight cases there were no siblings living in the same household.
<sup>q</sup> n=33.
<sup>r</sup> n=32.
Measures to avoid prolonged seizures and their consequences according to caregivers.

Table 4

| Measures                      | All children n (%) | Older children n (%) | Younger children n (%) | Chi square | p       | 'Severe' epilepsy n (%) | Chi square | p       | 'Less severe' epilepsy n (%) | Chi square | p       |
|-------------------------------|--------------------|----------------------|------------------------|------------|---------|-------------------------|------------|---------|-------------------------------|------------|---------|
| Any emergency seizure medicine | Yes, now (37)      | Earlier (5)          | Unknown (0)            | 0          | 0       | 15/18 (83)              | 0          | 0       | 22/24 (92)                   | 0          | 0       |
| Rectal diazepam               | 17 (40)            | 22 (52)              | 2 (4.8)                | 1 (2.4)    | 0       | 7/17 (41)               | 0          | 0       | 10/24 (42)                   | 0          | 0.001  |
| Buccal midazolam              | 27 (64)            | 11 (26)              | 4 (9.5)                | 0          | 0       | 11/18 (61)              | 0          | 0       | 16/24 (67)                   | 0          | 0.14   |
| Nasal midazolam               | 4 (9.5)            | 1 (2.4)              | 35 (83)                | 0          | 0       | 1/18 (5.6)              | 0          | 0       | 3/24 (12)                    | 0          | 0.62   |
| Seizure alarm                 | 12 (29)            | 8 (19)               | 22 (52)                | 0          | 0       | 4/16 (22)               | 0          | 0       | 8/24 (33)                    | 0          | 0.62   |
| Port-a-Cath                   | 11 (26)            | 0                    | 31 (74)                | 0          | 0       | 2/18 (11)               | 0          | 0       | 9/24 (38)                    | 0          | 0.08   |
| Home pulse oximetry           | 12 (29)            | 1 (2.4)              | 29 (69)                | 0          | 0       | 3/18 (17)               | 0          | 0       | 9/24 (38)                    | 0          | 0.14   |
| Home oxygen                   | 7 (17)             | 1 (2.4)              | 34 (81)                | 0          | 0       | 2/18 (11)               | 0          | 0       | 5/24 (21)                    | 0          | 0.68   |

Children born 2000-2009, n=18.
Children born 2010-2018, n=24.
Chi square was used for tests with all expected values >5.
Epilepsy severity, defined as 'severe/less severe' epilepsy, was investigated based on five items from the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) scale, and was classified as 'severe/less severe' based on a median split. Data on epilepsy severity was available in 41 children.
Fishers exact test was used for all tests with at least one expected value < 5.
Chi n = 42.
Chi n = 41.
Chi n = 40.
All children that had used nasal midazolam had also used buccal midazolam.

3.3. Measures to avoid prolonged seizures and their consequences

All 42 children had used rescue medications and 37/42 (88%) were currently using such medications (Table 4). Rectal diazepam had been used by 39/42 (93%) children and buccal midazolam by 38/42 (90%). Rescue medications were used between zero and 120 (median two) times every three months. They had been used more frequently in younger children (median five, range 0-120), compared to older children (median zero, range 0-12, p=0.006) and 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). Seizure alarms, mainly permanently mounted for use during sleep, had been used with 20/42 (48%) children. Thirteen (31%) children had used home pulse oximetry to detect hypoxia caused by seizures. Eight (19%) children had used home oxygen during seizures and 11/42 (26%) had a Port-a-Cath to facilitate intravenous access in case of SE.

4. Discussion

This is one of the first studies to comprehensively describe caregiver-reported seizure precipitants, measures employed to prevent seizures and limit seizure duration and consequences of prolonged seizures in children with Dravet syndrome (DS). All children in our study had reportedly experienced seizure precipitants and in all, measures had
been taken to prevent seizures. All had used emergency medicines. Results of the study thus indicate that caregivers identify a wide range of possible seizure precipitants and employ a range of measures to prevent/limit seizures.

4.1. Seizure precipitants

Febrile and afebrile infections, physical activity, tiredness, strong emotions, and crowds were all factors that had provoked seizures in more than 50% of children in our study, in line with findings from the study by Verbeek et al.\(^1\). In this Dutch study, seizures in children with DS were provoked by a higher number of seizure precipitants and a higher proportion of individuals were affected by each precipitant compared to other children with epilepsy and individuals with community-based epilepsy. In our study, caregivers reported that seizures had been provoked by warm weather in 69%, by sleep in 60%, and in 48% by exposure to reduced ambient temperature, such as cold weather or immersion in cold water. These are precipitants not specifically asked for by Verbeek et al.\(^1\). Submersion in water and change in external temperature has been reported as triggers in DS without further definition\(^2\). Reduced ambient temperature specifically leading to seizures is not described earlier and needs to be confirmed in other studies. Sleep and increased external temperature have been reported as precipitants in DS\(^2,20,21\), in line with results of the current study. However, heat has been reported to provoke seizures in less than 10% of individuals with other types of epilepsies\(^22-26\). Sleep has in other types of epilepsy been reported as a common seizure precipitant\(^23,25\), but also as a factor inhibiting seizures\(^25,26\). Tiredness was reported as a seizure trigger in 32/42 (76%) children and strong emotions in 27/42 (64%). This is in line with previous findings in different types of epilepsy, reporting tiredness, lack of sleep, emotional stress, and negative feelings among the most common precipitants\(^23,26\).

All children had experienced febrile infections and 93% had experienced afebrile infections as seizure triggering factors, confirming that seizures provoked by slight temperature changes without true fever, and of infections, as well as febrile status epilepticus (SE) are part of the core DS phenotype\(^27\). However, fever and general illness as precipitants seem to be less common in other types of epilepsy and have been reported as triggering factors in 14-25% of children and adults with epilepsy in tertiary epilepsy centers\(^22,24,25\). A higher proportion of younger children in our study had seizures triggered by afebrile infections, possibly because viral respiratory infections are more common in younger children\(^28\). A higher proportion of younger children had seizures triggered by reduced ambient temperature. A larger body surface area in relation to weight will lead to faster reduction of body temperature when exposed to reduced ambient temperature\(^29\), possibly leading to a higher susceptibility to seizure induction.

Bright light was a more common seizure inducing factor in children with ‘severe’ epilepsy but did not differ depending on age. This can be compared with the finding that constant bright light illumination has been described as a triggering factor in younger children with the most severe epilepsy in DS and disappeared in some children after the age of four years\(^3\). A photoparoxysmal response in DS has also been related to increased external temperature has been reported as precipitants in DS\(^2,20,21\), in line with results of the current study. However, heat has been reported to provoke seizures in less than 10% of individuals with other types of epilepsies\(^22-26\). Sleep has in other types of epilepsy been reported as a common seizure precipitant\(^23,25\), but also as a factor inhibiting seizures\(^25,26\). Tiredness was reported as a seizure trigger in 32/42 (76%) children and strong emotions in 27/42 (64%). This is in line with previous findings in different types of epilepsy, reporting tiredness, lack of sleep, emotional stress, and negative feelings among the most common precipitants\(^23,26\).

All children had experienced febrile infections and 93% had experienced afebrile infections as seizure triggering factors, confirming that seizures provoked by slight temperature changes without true fever, and of infections, as well as febrile status epilepticus (SE) are part of the core DS phenotype\(^27\). However, fever and general illness as precipitants seem to be less common in other types of epilepsy and have been reported as triggering factors in 14-25% of children and adults with epilepsy in tertiary epilepsy centers\(^22,24,25\). A higher proportion of younger children in our study had seizures triggered by afebrile infections, possibly because viral respiratory infections are more common in younger children\(^28\). A higher proportion of younger children had seizures triggered by reduced ambient temperature. A larger body surface area in relation to weight will lead to faster reduction of body temperature when exposed to reduced ambient temperature\(^29\), possibly leading to a higher susceptibility to seizure induction.

Bright light was a more common seizure inducing factor in children with ‘severe’ epilepsy but did not differ depending on age. This can be compared with the finding that constant bright light illumination has been described as a triggering factor in younger children with the most severe epilepsy in DS and disappeared in some children after the age of four years\(^3\). A photoparoxysmal response in DS has also been related to younger age at seizure onset and a more severe intellectual disability\(^12\).

4.2. Caregiver-reported measures to avoid seizures

In all children at least one measure had been taken to avoid seizures. Warm weather, physical activity, infections, tiredness and exposure to crowds were reported to be currently avoided by at least 50% of participants. As a comparison around 50% of young people, aged 14-22 years, with refractory epilepsy reported that they took steps to avoid seizures by measures such as relaxation and physical stimulation\(^3\). In adults with epilepsy one-third reported factors inhibiting seizures. The most common were positive feelings and focus\(^32\).

In our study measures taken to avoid infections to reduce seizure burden, in the child with DS included applying increased hand hygiene to all family members and siblings staying home from school to avoid infections. In five cases family members avoided contact with the child when they were infected, in some cases by moving out of the house. This is in line with another study where almost half of 219 families with children with DS had previously used similar or more stringent measures to protect against infections than the ones recommended during the Covid-19 pandemic\(^33\). According to a meta-analysis, increased hand-hygiene can reduce gastrointestinal and respiratory infections, and the most effective methods were hand-hygiene education and use of non-antibacterial soap\(^34\). As seizures in DS can be provoked by febrile infections\(^35,36\), increased hand-hygiene might reduce seizures.

The current number of preventive factors were higher in children with ‘severe’ epilepsy and infections were more frequently avoided. More of those children stayed home from school to avoid infections and more families of children with ‘severe’ epilepsy applied increased hygiene in the rest of the family to avoid infecting the child. Crowds were also significantly more frequently avoided in children with ‘severe’ epilepsy. It is likely that caregivers of children with a high frequency of seizures may decide to take more comprehensive seizure preventative measures. We cannot explain why precisely these measures were more commonly used. Reduced ambient temperature was more frequently avoided in younger children and was a significantly more common triggering factor in this age-group. Strong emotions were significantly more frequently avoided in younger children. It may be that parents of younger children with DS take more measures to avoid strong emotions as they feel that younger children are more likely to display emotions that can escalate quickly and thus lead to seizures. All these new findings need confirmation in further studies.

One quarter of all children had used intravenous immunoglobulin and/or antibiotic prophylaxis to prevent seizures by reducing infections. To our knowledge there are no other studies investigating the frequency of this measure in DS. Personal cooling devices had been used by around half the participants. Such devices were used more frequently in younger children possibly because seizures tend to be more severe in younger children\(^33,34\). Cooling vests were considered effective in a minority of patients by an American consensus panel\(^31\). But there are to our knowledge no other studies investigating how effective these devices are to prevent seizures.

4.3. Measures to limit occurrence of prolonged seizures and their consequences

Buccal/nasal midazolam had been used by 90% of children in our study and by 68% in an international survey with 256 individuals with DS of all ages\(^34\). As a comparison, rectal diazepam had been used by 94% in our study, and in an equal percentage in the survey, while buccal/nasal lorazepam had been used by 70% in the survey and by none of our participants. Lorazepam is not available in Sweden, which likely explains a higher usage of buccal/nasal midazolam in our study. The use of emergency medications was more frequent in children with ‘severe’ epilepsy, and in the younger age group, in line with the reports that seizure severity and tendency to develop SE in DS might diminish with age during childhood/adolescence\(^27,35\). In North America rectal diazepam is considered optimal rescue medication in children < 6 years and buccal/nasal midazolam in all ages\(^31\). In our study there was no difference in the present use of rectal diazepam depending on age, being around 40% in both age groups. The use of rectal diazepam might have remained high because of a reluctance to discontinue it even after six years of age due to perceived efficacy.

Nineteen percent had used home oxygen and 31% home pulse oximetry. National Institute for Health and Care Excellence (NICE) recommends high flow oxygen in the management of seizures\(^36\). However, only four small studies have investigated this issue, showing reduced duration of respiratory dysfunction and reduced suppression of EEG but little or no effect on seizure duration\(^36\). Port-a-Cath can be used for rapid.
Seizure detection devices, mainly for use in bed during sleep, had been used by half of all participants. In Sweden a higher percentage of children with DS use such devices compared to children with other types of epilepsy due to a high frequency of SE and seizure related mortality, including sudden unexpected death in epilepsy (SUDEP). Seizure-detection devices might provide an extra back-up at night, improving the sleep of the caregivers and detect previously unnoticed seizures. Such devices might also offer opportunities to prevent SUDEP, by timely response by caregivers to bilateral tonic clonic seizures. However, it is uncertain whether the devices result in clinically meaningful outcome for patients, and false-alarm and undetected seizures are problems. Out of 23 devices identified in a review, only seven had published peer-reviewed performance data. The median reported sensitivity to detect bilateral tonic clonic seizures was around 90%, and the false alarm rate 2.5–24 hours in wrist-worn devices. The two bed movement sensors investigated had a lower sensitivity ranging from 11-63%. The method has been used in other studies investigating seizure precipitants. Thus, self-reported information on seizure precipitants should be interpreted with caution. However, the high frequency of patients and caregivers reporting seizure precipitants, especially in children with DS, makes it unlikely that the occurrence of precipitants simply is a misconception. It is important to verify the frequency of different precipitants in prospective studies with control groups consisting of children with other epilepsy syndromes and adults with DS. Some caregivers spontaneously reported that they avoided spontaneous family meetings or favorite activities to avoid making the child too excited, as excitement usually provoked a seizure. Measures such as avoiding strong feelings like happiness, avoiding sending the child and siblings to school in case of infections, and isolating the child from other family members when they are sick, negatively affects the life of the child and of the whole family. Modification of seizure precipitants can reduce or even eliminate seizures in children and adults with drug resistant epilepsy according to previous papers. Thus, some measures employed by caregivers might reduce seizure burden and SE, leading to improved safety and health-related quality of life (HRQoL). But some measures may adversely affect family functioning and HRQoL. There is an urgent need for further studies investigating the effectiveness of different measures to control seizures, and how these measures affect HRQoL. Some precipitants might interact with or depend on each other. Exposure to cold water or crowds might for example lead to strong emotions. A strong relation has also been found between stress, fatigue and lack of sleep as seizure precipitants, suggesting that they act through the same mechanism. Consequently, there is a need to explore the relationship between different seizure precipitants and possible underlying factors. Some measures like use of air conditioning, which otherwise is unusual in Sweden, and use of seizure alarms and home oxygen lead to an increased economic cost for the family and/or the society underlining the importance to evaluate the effectiveness of those devices.

5. Conclusion

Caregiver-reported seizure precipitants are very common in DS and caregivers employ several measures to avoid seizures, as well as prolonged seizures and their consequences. Some measures have the potential to negatively affect HRQoL. There is a need for further studies employing robust prospective study designs to confirm our results and interventional studies to investigate the effectiveness of measures to prevent seizures and how these measures affect HRQoL for the child and the family.

Declaration of Competing Interest

The authors confirm that they have no interests that might be perceived as posing a conflict or bias.

Acknowledgements

The authors thank the study participants and their families. We thank the Swedish pediatric neurologists and epilepsy nurses who invited families to participate in the study. This study was supported by grants from the Swedish state under the agreement between the Swedish Government and the county councils, the ALF-agreement 956787, the Margarethahemmet, the Linnea and Josef Carlsson and Petter Silver-skild foundations, Dravet Syndrome Association Sweden, and the National Center for Rare Diseases West. The funders had no role in the writing of the articles. Conflicts of interest; none.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.09.018.

References

[1] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21.
[2] Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. Adv Neurol 2005;95:71–102.
[3] Claes L, Del-Favero J, Ceulemans B, Lagae L, van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1227–32.
[4] Jansson JS, Hallbok T, Reilly C. Intellectual functioning and behavior in Dravet syndrome: a systematic review. Epilepsy Behav E 2020;108:107079.
[5] Symonds JD, Zuberi SM, Stewart K, McLellan A, O’Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort Brain J Neurol. 2019 Aug 1;142:2303–18.
[6] Dravet C, Bureau M, Dalla Bernardina B, Guerini R. Severe myoclonic epilepsy in infancy (Dravet syndrome) 30 years later. Epilepsia. 2011. 52 Suppl 2:1-2.
[7] Oguni H, Hayashi K, Awaya Y, Fukuyama Y, Osawa M. Severe myoclonic epilepsy in infants—a review based on the Tokyo Women’s Medical University series of 84 cases. Brain Dev 2001;23:736–48.
[8] Knupp KG, Scabrero S, Wilkening G, Juarez-Colunga E, Kempe A, Dempsey A. Parental perception of comorbidities in children with dravet syndrome pediatric. Neurology 2017;76:605-S.
[9] Verbeek NE, Wassenaar M, van Campen JS, Sonnema A, Gunning B, Knoers N, et al. Seizure precipitants in Dravet syndrome: What events and activities are specifically provocative compared with other epilepsies? Epilepsy Behav E 2015;47:39–44.
[10] Verbeek N, Kastelein-Noord Trenite D, Wassenaar M, van Campen J, Sonnema A, Gunning WB, et al. Photo-sensitivity in Dravet syndrome is under-recognized and related to prognosis. Clin Neurophysiol 2017;128:323–30.
[11] Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a North American consensus panel pediatric. Neurology 2017;68:18–34.e13.
[12] Ceulemans B. Overall management of patients with Dravet syndrome Dev. Med Child Neurol 2011;53(Suppl 2):19–23.
[13] Schubert-Bast S, Wolf M, Wiener-Kruel A, von Spiczak S, Trollmann R, Riefler P, et al. Seizure management and prescription patterns of anticonvulsants in Dravet syndrome: European Journal of Epilepsy 103 (2022) 3–10
