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ORIGINAL ARTICLE

Response to treatment and outcomes of infantile spasms in Down syndrome

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Abstract

Aim: To estimate the prevalence, and evaluate presentation, treatment response, treatment side effects, and long-term seizure outcomes in all known cases of children with Down syndrome and infantile spasms on the island of Ireland.

Method: This was a 10-year retrospective multicentre review of clinical records and investigations, focusing on treatment response, side effects, and long-term outcomes.

Results: The prevalence of infantile spasms in Down syndrome was 3.0% during the study period. Fifty-four infants were identified with median age of spasm onset at 201 days (interquartile range [IQR] 156–242). Spasm cessation was achieved in 88% (*n*=46) at a median of 110 days (IQR 5–66). The most common first-line medications were prednisolone (*n*=20, 37%), vigabatrin (*n*=18, 33.3%), and sodium valproate (*n*=9, 16.7%). At follow-up (median age 23.7mo; IQR 13.4–40.6), 25% had ongoing seizures and 85% had developmental concerns. Treatment within 60 days did not correlate with spasm cessation. Seventeen children (31%) experienced medication side effects, with vigabatrin accounting for 52%.

Interpretation: Prednisolone is an effective and well-tolerated medication for treating infantile spasms in Down syndrome. Despite the high percentage of spasm cessation, developmental concerns and ongoing seizures were common.

Trisomy 21 or Down syndrome is the most common chromosomal abnormality reported worldwide. The Republic of Ireland has the highest birth prevalence in Europe at 20.79 per 10 000 live births compared with 5.72 per 10 000 live births in Europe.[1] Children with Down syndrome are a complex population with multisystem involvement and an increased burden of congenital anomalies and acquired conditions.[2] Children and adults with Down syndrome have an increased lifetime risk of epilepsy. However, there are no prospective studies providing an accurate estimate of the lifetime prevalence. Various groups have estimated prevalence to be 1.6% to 23.1%, and aggregate data estimate prevalence to be 5.8%.[3–5] Despite the variability in prevalence, infantile spasms are consistently the most frequent epilepsy syndrome reported in Down syndrome, estimated to occur in up to 13% of cases.[6] Infantile spasms in Down syndrome are associated with

Abbreviations: ACTH, Adrenocorticotropic hormone; ICISS, International Collaborative Infantile Spasms Study.

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poorer neurodevelopmental outcomes, increased risk of autism spectrum disorder, and intellectual disability.[3,7,8]

Treatment approaches of infantile spasms differ worldwide owing to regional drug preferences, resource availability, and cost. The International Collaborative Infantile Spasms Study (ICISS) demonstrated superiority of combination hormonal treatment (prednisolone or adrenocorticotropic hormone [ACTH]) and vigabatrin over hormonal treatment alone: 72% vs 57% spasm cessation at 4 weeks.[9] At 18-month follow-up, treatment modality did not influence long-term outcomes.[10] Despite this, early clinical response has been associated with improved epilepsy and developmental outcomes, highlighting the need for prompt initiation of treatment.[11] The ICISS Down syndrome subcohort analysis (n=37) reported similar outcomes, with 55% responding to hormonal treatment alone, compared with 53% on combination vigabatrin and hormonal treatment. Thus, the first-line choice of treatment remains controversial for the population with Down syndrome.

We reviewed all known cases of children with Down syndrome and infantile spasms on the island of Ireland. Our aim was to evaluate presentation, treatment response, treatment side effects, and the proportion who achieved long-term seizure freedom.

What this paper adds

- The prevalence of infantile spasms in Down syndrome was 3%.
- Prednisolone is an effective first-line medication (60% spasm cessation).
- Treatment within 60 days did not correlate with spasm cessation.
- The long-term risk of epilepsy including ongoing spasms was 25%.

METHOD

We used a retrospective chart review of all cases of infantile spasms in children diagnosed with Down syndrome between January 2010 and June 2020. This was a multisite review involving seven paediatric neurology centres on the island of Ireland. Ethical approval was granted by the research and ethics committee at Children's Health Ireland at Temple Street, Dublin, Ireland (reference 20.021).

Inclusion criteria included a diagnosis of Down syndrome with a history of infantile spasms and electroencephalogram (EEG) showing hypsarrhythmia or modified hypsarrhythmia. The term 'hypsarrhythmia' was used when the following criteria were met: high-voltage slowing, disorganized background, and multifocal sharp waves.[12] The term 'modified hypsarrhythmia' applied to the following patterns or variations on hypsarrhythmia: hypsarrhythmia with increased interhemispheric synchronization; asymmetrical hypsarrhythmia; hypsarrhythmia with a consistent focus of abnormal discharge; hypsarrhythmia with episodes of attenuation; and hypsarrhythmia comprising primarily high-voltage slow activity with little sharp-wave or spike activity.[13] Infantile spasms had to start before 2 years of age. Children whose spasms were focal on EEG were excluded. A history of developmental regression was not necessary for inclusion. Spasm cessation was determined clinically and defined as the permanent cessation of spasms with no relapse seen during the follow-up period. No national standardized treatment algorithm is in use for infantile spasms in Ireland. Choice of medication and dosing regimen were dependent on the treating clinician and institution. No formal development assessment was undertaken, and developmental outcomes reported were the subjective assessment of the treating clinician. Developmental delay was defined as a greater delay than would be expected in the typical development (cognitive, motor, social) of a child with Down syndrome. Each centre completed a case note review and returned anonymized data through a standardized study proforma.

We used SPSS (version 26; IBM Corp., Armonk, NY, USA) for statistical analysis with significance set at $p<0.05$. Parametric tests were performed where data were normally distributed, and non-parametric tests if data were not normally distributed. When analysing the effect of lead time to treatment on outcomes, a cut-off of 60 days was used. The period prevalence of infantile spasms in Down syndrome was calculated on the basis of the total number of cases of infantile spasms identified and the number of live births of infants with Down syndrome over the study period in the Republic of Ireland only.

RESULTS

Demographics

Fifty-four children fulfilled the inclusion criteria. There were 33 males and 21 females. Demographic details are outlined in Table 1. No child had a history of perinatal hypoxia. Six children were born at late preterm gestational ages (32–35wks) and two extremely preterm (24^{+5}wks and 25^{+4}wks). Comorbidities were present in 97%, most commonly congenital cardiac disease (n=32, 59%). The median length of follow-up was 23.7 months (interquartile range [IQR] 13.4–40.6).

Presentation of spasms

As determined by parental report, spasm onset occurred at a median age of 201 days (IQR 156.0–242.5) with a median age at presentation of 239 days (IQR 191.5–319.5). The median time from onset to presentation was 28 days (IQR 10.0–69.5). Developmental regression was reported in 56% (n=31) at presentation, most frequently in social skills (30%, n=16) or combined motor and social skills (25%, n=14).

TABLE 1 Demographic characteristics of cohort with Down syndrome and infantile spasms (*n*=54)

Demographics	*n*=54 (%)
Sex	
Male	33 (61)
Female	21 (39)
Genetic diagnosis	
Trisomy 21	51 (94)
Other (1=translocation, 1=ring chromosome 20, 1=trisomy 5 & partial trisomy 21)	3 (6)
Comorbidities	
Cardiac	32 (59)
Respiratory	11 (20)
Congenital hypothyroidism	9 (17)
Preterm birth	8 (15)
Gastrointestinal	6 (11)
Haematological	3 (6)
Other	4 (7)
Regression at presentation	
Total	31 (56)
Social skills	16 (30)
Motor and social skills	14 (25)
Motor skills	1 (2)
Spasm characteristics	
Median age at spasm onset (IQR)	201d (156.0–242.5)
Median age at presentation (IQR)	239d (191.5–319.5)
Median lead time to presentation (IQR)	28d (10.0–69.5
Follow-up	*n*=52 (%)
Median length of follow-up (IQR)	23.7mo (13.4–40.6)
Median age at last follow-up (IQR)	30mo (24.0–49.0)
Spasm resolution	46 (88)
Ongoing seizures	13 (25)
Lennox–Gastaut syndrome	2 (3.8)
Antiseizure medication	22 (42)
Developmental delay	44 (85)
Autism spectrum disorder	4 (8)
EEG	*n*=54 (%)
EEG at presentation	
Classical hypsarrhythmia	37 (69)
Modified hypsarrhythmia	17 (31)
First repeat EEG	
Encephalopathy resolved	27 (50)
Classical hypsarrhythmia	12 (22)
Modified hypsarrhythmia	12 (22)
Results unavailable	3 (6)
Imaging	*n*=42 (78%) (5 both CT and MRI)
CT brain	*n*=10
Median age at imaging (IQR)	9mo 18d (8mo 16d– 12mo 27d)
Abnormal CT	5 (50)[a]
Volume loss	4
Low attenuation brainstem vigabatrin-related	1
MRI brain	*n*=37
Median age at MRI (IQR)	9mo 6d (6mo 5d– 14mo 12d)
Abnormal MRI	17 (46)[a]
Vigabatrin-related changes	6
Volume loss	5
Cortical malformation	3
Other	4

Abbreviations: CT, computed tomography; EEG, electroencephalography; IQR, interquartile range; MRI, magnetic resonance imaging.

[a]Calculated on the basis of the number of scans performed rather than total numbers.

Electrophysiology

Initial EEG showed classical hypsarrhythmia in 69% (*n*=37) with modified hypsarrhythmia in 31% (*n*=17). A repeat EEG result was available for 94% (*n*=51) with repeat EEG recorded at a median of 23 days (IQR 14.5–50.0) following the initial EEG. Hypsarrhythmia had resolved in 50% (*n*=27) and there was a normal EEG in 35% (*n*=19).

Neuroimaging

Neuroimaging was performed in 78% (*n*=42), and findings are summarized in Table 1. The decision to undertake imaging and choice of imaging modality varied by study centre. Five infants had both computed tomography (CT) and magnetic resonance imaging (MRI) of the brain performed. Abnormal findings were identified in 5 out of 10 CT and 17 out of 37 MRI. Imaging changes associated with vigabatrin were the most frequent finding, occurring in 6 out of 11 whose imaging was performed while prescribed vigabatrin. Typical changes associated with vigabatrin were bilateral restricted diffusion affecting the deep grey matter (Fig. 1). Volume loss was the second most common abnormality (*n*=5) in the infants, all of whom had started prednisolone before neuroimaging.

Spasm cessation

Spasm resolution occurred in 88% (*n*=46). The median time to spasm cessation from the onset was 110 days (IQR 41.7–196.0) and from start of medication 30 days (IQR 5.0–153.0). The median age at spasm cessation was 335.5 days (IQR 266.3–468.0). By days 30 and 60 of treatment, 42.6% (23 out of

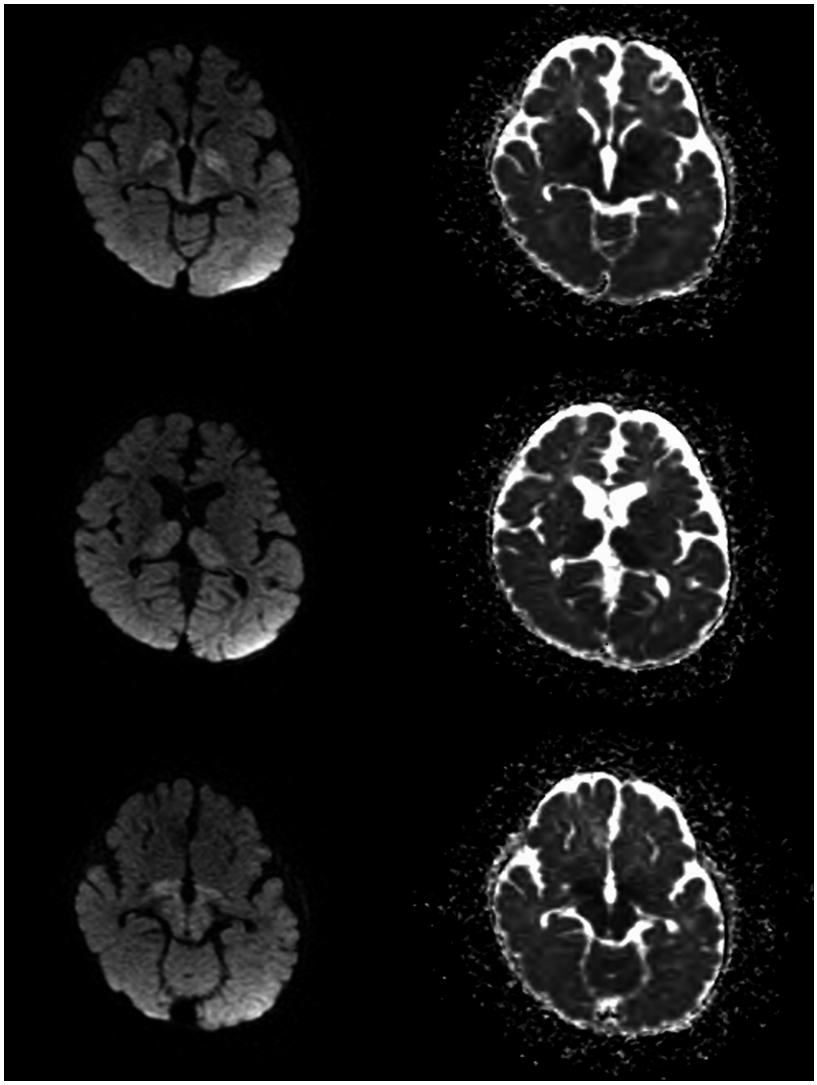

FIGURE 1 Abnormal restricted diffusion in the bilateral globus pallidi and thalami extending into the cerebral peduncles and dorsalis pons in a child on vigabatrin 150mg/kg/d

54) and 59.3% (32 out of 54) respectively, had achieved spasm cessation. Treatment within 60 days of spasm onset did not correlate with achieving spasm cessation (84.2% vs 93.3%, p=0.377) or time to achieve spasm cessation (30.0d vs 30.2d, p=0.775). Ongoing seizures (including spasms) were more likely in those who started treatment within 60 days (31.6% vs 6.7%; p=0.058).

Spasm cessation occurred in 44% (n=24) following first-line medication. Those given combination prednisolone and vigabatrin as a first-line medication had the shortest time to spasm cessation at a median of 4 days (IQR 1.5–6.5), compared with medians of 6.5 days (IQR 4–15.75) for prednisolone and 30 days (IQR 1–33) for vigabatrin.

Treatment

A median of two medications (IQR 1–3, range 1–9) was required to achieve spasm cessation. Nine different medications resulted in spasm cessation (Table S1).

First-line medication

Information about first-line medication choice and success is outlined in Table 2. Initial medication choice varied by institution and the date of presentation. At the start of the study period, sodium valproate was prescribed frequently. The most frequent first-line medication was prednisolone (n=20), followed by vigabatrin (n=18), sodium valproate (n=9), combination prednisolone and vigabatrin (n=6), and ACTH (n=1). Combination prednisolone and vigabatrin was successful in 83% (n=5) compared with prednisolone only (60%, n=12) and vigabatrin only (28%, n=5). However, the number treated with combination prednisolone and vigabatrin was small, with only six in this cohort.

Second- and third-line medication

Second- and third-line medication choice was variable. Second-line medications prescribed were vigabatrin (n=13),

TABLE 2 Response to, and outcomes by, first-line medication

	Prednisolone only (*n*=20)	Vigabatrin only (*n*=18)	Sodium valproate only (*n*=9)	Prednisolone and vigabatrin (*n*=6)	ACTH only (*n*=1)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
After first medication only					
Spasm cessation	12 (60)	5 (28)	1 (11)	5 (83)	1 (100)
Days to spasm cessation (median [IQR])	6.5 (4.0–15.75)	30 (1–33)	7	4 (1.5–6.5)	5
Median dose in successful group (mg/kg/day) (IQR)	4.0 (3.6–5.0)	102.4 (70.0–145.0)	20	3.8/72 (4–6/50–100)	0.5mg alternate days
Side effects	3 (15)	5 (28)	1 (11)	3 (50)	0
At follow-up					
Resolution of infantile spasms	19 (95)	13 (72)	9 (100)	6 (100)	1 (100)
Ongoing seizures	3 (15)	3 (17)	2 (22)	1 (17)	0
Developmental concerns	16 (80)	14 (78)	8 (89)	5 (83)	1 (100)
Mean number of medications	2.6 (1–10)	2.7 (1–6)	3.1 (1–9)	2.2 (2–3)	1

Abbreviations: ACTH, adrenocorticotropic hormone; IQR, interquartile range.

prednisolone (*n*=7), sodium valproate (*n*=2), clonazepam (*n*=2), ACTH (*n*=1), and ACTH/prednisolone (*n*=1). Spasm cessation was achieved in two children (1 with prednisolone; 1 with ACTH). Of the medications used as third-line and subsequent options, zonisamide resulted in spasm cessation in 4 out of 7 followed by vigabatrin (2 out of 4), and sodium valproate (4 out of 11). Further information about third-line and subsequent medications is available in Table S1.

Side effects

Twenty-five separate side effects were documented in 17 children. Vigabatrin was responsible for most (*n*=10), followed by combination prednisolone and vigabatrin (*n*=6), prednisolone (*n*=4), sodium valproate (*n*=2), and other (*n*=3). Side effects associated with vigabatrin (*n*=13) were restricted diffusion on MRI (*n*=6; Fig. 1), irritability (*n*=2), sedation (*n*=2), movement disorder (*n*=2), and feeding difficulty (*n*=1). Prednisolone was associated with decreased appetite, weight gain, irritability, and hypertension. There were two admissions to intensive care units after the start of medications for infantile spasms. One child developed respiratory syncytial virus bronchiolitis on vigabatrin monotherapy. The second child was admitted with presumed status epilepticus and subsequently diagnosed with a vigabatrin-induced hyperkinetic movement disorder. Both children who developed vigabatrin-induced hyperkinetic movement disorder were on vigabatrin for 6 weeks before symptom onset and treated with doses above 100mg/kg/d. Both had restricted diffusion on MRI and achieved total resolution of symptoms following vigabatrin wean.

Long-term outcomes

The median age at follow-up was 30 months (IQR 24–49). Two children died unrelated to infantile spasms. There were ongoing seizures (including spasms) in 25% (13 out of 52), 42% (22 out of 52) on antiseizure medication, and developmental concerns in 85% (44 out of 52) (Table 1). In those requiring ongoing antiseizure medication, reasons included ongoing seizures (*n*=13), history of spasm cessation less than 6 months previously (*n*=2), and persistent abnormal EEG findings (*n*=2). Two children had a confirmed diagnosis of autism spectrum disorder, with two awaiting assessment. Outcomes by initial medication choice are summarized in Table 2.

Prevalence in Down syndrome

The total number of recorded births of children with Down syndrome in the Republic of Ireland between January 2010 and June 2020 was 1714. The total number of infantile spasms in Down syndrome cases recorded in the Republic of Ireland in that time was 51. Thus, the prevalence of infantile spasms in Down syndrome was 3.0%.

DISCUSSION

To our knowledge, this is the largest cohort of children with Down syndrome and infantile spasms published so far (*n*=54). Although prescribing practices varied among study centres, 88% (46 out of 52) of children had resolution of spasms. Prednisolone was the most commonly prescribed medication overall (*n*=35) and achieved spasm cessation in 16 out of 35. The prevalence of infantile spasms was 3% in our population with Down syndrome, which is slightly higher than the median lifetime prevalence of 2.1% (range 0.4–12.8) of epileptic spasms recently reported.[5]

Studies focusing on treatments and outcomes of infantile spasms in cohorts with Down syndrome are lacking. Previous studies have reported on ACTH, sodium

valproate, and vigabatrin only as first-line medications. The success rates, cohort sizes, and duration of follow-up varied.[8,14–16] Overall, 44% (*n*=24) achieved spasm cessation after the first medication (Table 2). In our study, prednisolone was the most frequently prescribed first-line medication (*n*=20), achieving spasm cessation in 60% (12 out of 20). This is comparable to the results of Armstrong et al. (*n*=20) and the ICISS Down syndrome subgroup analysis (*n*=37), with rates of 60% and 54% respectively.[17,18] Vigabatrin was the second most common first-line agent, with cessation of spasms in 28% (5 out of 18), similar to the 21% (5 out of 24) success rate reported by Datta et al.[19] Our findings are also in agreement with the ICISS cohort, who reported the addition of vigabatrin was beneficial in only 1 out of 7 who did not respond to first-line prednisolone.[17,18] Only six children had both combination prednisolone and vigabatrin as first-line treatment in our cohort, with an 80% response although three out of six developed side effects, including one who required admission to an intensive care unit. Sodium valproate was commonly prescribed in the first 5 years of the study with a poor response (1 out of 9). Therefore, we provide further evidence to support the use of prednisolone only as first-line treatment of infantile spasms in Down syndrome.

Age at spasm onset and presentation were comparable to previous reports, with a median of age at onset of 201 days (IQR 156.0–242.5) and a median age at presentation of 239 days (IQR 191.5–319.5).[3,8,15–17] Previous reports suggested that children with Down syndrome may have better outcomes due to earlier presentation.[20] Although we did not compare time to presentation with a population without Down syndrome, we demonstrate marked variability in time to presentation between 1 and 494 days (median 28.0, IQR 10.0–69.5). Eisermann et al. reported that a longer lead time to treatment (>60d) was associated with a longer time to spasm cessation ($p<0.002$), poorer developmental outcomes ($p<0.004$), increased risk of epilepsy ($p=0.03$), and features of autism spectrum disorder ($p<0.006$).[11] These associations were not replicated in our cohort (Table 3), as a lead time of greater than 60 days was associated with higher spasm cessation (93.3% vs 84.2%, $p=0.377$) and fewer ongoing seizures (6.7% vs 31.6%, $p=0.058$) (Table 3).

In our cohort, 25% (*n*=13) had persistent seizures, including spasms. Previous papers have reported ongoing seizure rates between 0% and 30%.[8,14,21,22] Our median length of follow-up was 23.7 months (IQR 13.4–40.6), longer than other groups, thus capturing the long-term risk of developing epilepsy. In the study reporting an incidence of 0%, median follow-up was only 9 months.[21] Although it is perceived that children with Down syndrome and infantile spasms have better long-term outcomes compared with those with other aetiologies of infantile spasms, clinicians must be cautious when counselling parents as one in four developed epilepsy in our cohort, higher than previously reported.

Neuroimaging was performed in 78% (*n*=42) and reported as abnormal in 19 out of 42. In 6 out of 19, abnormal imaging was a consequence of vigabatrin treatment (Fig. 1). Among our cohort, 6 out of 42 had potentially relevant imaging abnormalities: cortical malformation (*n*=3), porencephalic cyst (*n*=1), bilateral grade three intraventricular haemorrhage (*n*=1), and post-meningitis changes (*n*=1). Three of the eight children with ongoing spasms had relevant findings, a likely contributing factor to treatment failure (Table S2). This proportion of abnormal imaging is similar to a previous review, which reported abnormal imaging in 42%, with only 16% having a potentially relevant structural or acquired abnormalities.[23] Trowbridge et al. found abnormal neuroimaging (congenital or acquired) was associated with refractory epilepsy and a need for antiseizure medications (5 out of 6 compared with 3 out of 11) in patients with Down syndrome who also had infantile spasms.[23] Given that only 14% had potentially contributory imaging findings, unless there are other clinical concerns such as relevant antenatal history, focal EEG findings, or an evolution to focal spasms, neuroimaging is unlikely to alter clinical management.

No previous publications have reviewed the tolerability to medications for infantile spasms in Down syndrome. In our cohort, there were 24 reported side effects from all medications experienced by 17 children. No deaths were attributed to medications. Vigabatrin was responsible for most side effects at 52% (*n*=13), most frequently restricted diffusion on MRI (*n*=6), a recognized dose-dependent side effect of vigabatrin.[24] Restricted diffusion occurred in 6 out of 39 of those who received vigabatrin at any time during the study but occurred in 6 out of 11 of those whose imaging was done while on vigabatrin. This is more than the 30.9% previously reported to have restricted diffusion following vigabatrin treatment for infantile spasms.[24] Children with Down syndrome may be more susceptible to vigabatrin changes. A recent meta-analysis identified

TABLE 3 Comparison of presentation and outcomes dependent on lead time to treatment

	Lead time <60d, *n*=38	Lead time >60d, *n*=15	*p*
Male:female, *n* (%)	21:17 (55.3:44.7)	11:4 (73.3:26.7)	0.060
Median days to presentation (IQR)	19 (5.8–30.5)	96.0 (77.0–133.0)	0.000
Regression at presentation, *n* (%)	21 (55.3)	10 (66.7)	0.448
Spasm cessation, *n* (%)	32 (84.2)	14 (93.3)	0.377
Median time to spasm cessation after starting treatment (IQR)	30d (4.3–174.8)	30d (6.5–60.0)	0.775
Ongoing seizures (including spasms), *n* (%)	12 (31.6)	1 (6.7)	0.058
Developmental concerns, *n* (%)	32 (84.2)	11 (73.3)	0.362

Note: One infant had incomplete data and is thus not included in this analysis.
IQR, interquartile range.

reversible changes in 88% of 57 infants with multiple aetiologies identified from 12 articles.[25] Twelve of these patients had clinical symptoms (encephalopathy and movement disorder) temporally associated with vigabatrin-related MRI signal changes which resolved after cessation of vigabatrin. This, in combination with reports of vigabatrin-associated non-radiological and non-ophthalmological adverse effects (sleep disorders and irritability) occurring in 23% of infants, suggests prednisolone monotherapy should remain first-line until further evaluation of the safety and side effect profile of vigabatrin is undertaken in this cohort.[25] It is possible that in our cohort some side effects associated with prednisolone, for example weight gain and irritability, may not have been documented as clinicians expected this and thus did not consider it a side effect. This limitation aside, prednisolone seems to be well tolerated.

The high incidence of comorbidities (97%) is not unexpected in this population. It is important to acknowledge that determining the potential contribution of comorbidities to spasm presentation and outcome is difficult, given that children with Down syndrome are already known to be at a higher risk of developing infantile spasms. In our cohort, among children with ongoing spasms and adverse developmental outcomes, there was no history of preterm birth, perinatal hypoxia, or significant cardiac comorbidities. Comorbidities reported included adenovirus meningitis preceding spasm onset (*n*=1), Hirschsprung disease (*n*=2), duodenal atresia (*n*=2), patent ductus arteriosus (*n*=5), atrial septal defect (*n*=2), and congenital hypothyroidism (*n*=2). With the exception of the adenovirus meningitis, it is unlikely the other comorbidities contributed to ongoing spasms.

There is limited available literature reporting on the use of zonisamide to treat infantile spasms in Down syndrome.[26] There was relative success of zonisamide achieving spasm cessation when used as an add-on medication in our cohort (4 out of 7). In the four who responded to zonisamide, it was used as fifth- and sixth-line options, in combination with levetiracetam or sodium valproate in three. Although the natural history of spasms suggests they may often gradually resolve with time, our cohort required a median of two medications (IQR 1–3, range 1–9) to achieve spasm cessation, with 17 out of 46 requiring at least three medications. The high number of medications frequently required suggests that zonisamide is likely to have contributed more to spasm cessation than cessation from natural history alone. This is a novel finding and warrants further investigation, as it may provide a potential option in children who are unresponsive to multiple medications with a good side effect profile.

Like prednisolone, ACTH is a well-established hormonal treatment of infantile spasms and has been documented as an effective treatment option in Down syndrome.[15] In our cohort, ACTH was only prescribed in three infants. Owing to the small numbers and lack of recent experience using ACTH, we cannot draw conclusions about its use. Prednisolone is readily available, well tolerated, orally administered, and demonstrates similar efficacy to ACTH in cohorts without Down syndrome.[27] Cost considerations are also an important factor given the marked difference in cost-effectiveness between high-dose prednisolone, which has an incremental cost-effectiveness ratio of US$333, and ACTH, which costs US$1 432 200 per case of spasms resolved.[27]

The ketogenic diet is an effective and safe treatment option for drug refractory epilepsies in infancy.[28] Evidence of ketogenic diet use for infantile spasms in Down syndrome is limited to small numbers of cases (*n*=5), reported as part of larger cohorts.[29–31] In our cohort, the ketogenic diet was used successfully in a single child, as a fifth-line treatment option in combination with sodium valproate and zonisamide. Given its high reported efficacy in other refractory infantile epilepsies, the ketogenic diet is likely to be an important treatment option in treating infantile spasms in Down syndrome and perhaps should be considered sooner in this cohort.

The pathogenesis of infantile spasms in Down syndrome is probably due to a complex interaction of altered neuronal ion channels and/or neurotransmitter function. Mouse models of Down syndrome are attempting to establish the pathogenesis and identify potential treatment options. In the Ts65Dn mutant mouse (Ts), an infantile spasm phenotype can be induced by $GABA_B$ (γ-aminobutyric acid) agonists. Over-expression of GIRK2 in the Ts-mouse brain is necessary for the production of the GABA-agonist-induced infantile spasms phenotype.[32] Further work has demonstrated that additional, as yet unknown, factors are also involved.[33]

The main limitation of our study is its retrospective nature. Other limitations include a lack of standardized medication dosing, timing of repeat EEG, or developmental follow-up. Indeed, developmental outcomes were subjective and based on clinical reports, rather than standardized methods used by other groups.[3,8,17] Developmental outcomes are difficult to report reliably in a retrospective study. This difficulty is amplified in a population with variable developmental trajectories even in the absence of an epileptic encephalopathy.

CONCLUSION

To our knowledge, this is the largest cohort of children with Down syndrome and infantile spasms (*n*=54) published so far. Prednisolone is an effective medication in this cohort, resulting in spasm cessation in 60% when used as a first-line medication. Although success is also reported with combination prednisolone and vigabatrin, the numbers included in this study are small. Prednisolone was well tolerated, and vigabatrin was responsible for half of all reported side effects. Despite the reported high spasm cessation (88%), developmental concerns and ongoing seizures (including spasms) were common. We conclude that prednisolone monotherapy should remain as the first-line treatment of infantile spasms in Down syndrome.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: List of successful medications with number of children who responded at each time point.
Table S2: Imaging findings in resolved and unresolved cases.

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