

Commentary: Does First-Line Treatment Impact Outcomes in Trisomy 21-Associated Infantile Epileptic Spasms Syndrome?

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Keywords

Infantile spasms, Epileptic spasms, Down syndrome, Trisomy 21, Lennox-Gastaut syndrome, Adrenocorticotrophic hormone, Prednisolone, Vigabatrin

Introduction

Trisomy 21 (T21) is the most common chromosomal disorder and is associated with a substantially increased risk of epilepsy, affecting approximately 5–10% of children [1,2]. Among infants with T21, infantile epileptic spasms syndrome (IESS) is the most common epilepsy syndrome of the first year of life, with a reported prevalence of 0.6–13%, approximately 100-fold higher than in the general population [3,4]. The occurrence of IESS adds an additional burden to a population already at risk for neurodevelopmental impairment, making early recognition and effective treatment particularly important [2,5,6].

As with IESS more broadly, first-line treatment in T21 typically consists of hormonal therapy (adrenocorticotrophic hormone [ACTH] or oral corticosteroids) or vigabatrin [7]. In practice, the choice between the two is shaped as much by institutional patterns, drug availability, cost and by the evidence itself, producing considerable variation across centers and countries [8]. Although accumulating data suggest that children with T21 respond particularly well to hormonal therapy [2,5,9–17], whether it is superior to vigabatrin for short- and long-term outcomes, including spasm cessation, relapse, subsequent epilepsy, and neurodevelopment, remains uncertain. To address this clinically important question, Cao et al. conducted a multicenter retrospective study comparing first-line hormonal therapy with vigabatrin in children with

T21-associated IESS. Their cohort is notable for including the largest number of vigabatrin-treated children reported to date, offering an opportunity to compare the two strategies directly [8].

Response to First-Line Treatment

Although both hormonal therapy and vigabatrin are recommended first-line treatments for IESS, including in children with T21, the available evidence generally supports hormonal therapy as an important first-line option, while the relative efficacy of these treatments in T21 remains uncertain. An aggregate review of studies in IESS more broadly reported response rates of approximately 81% with ACTH or corticosteroids compared with 55% with vigabatrin [3]. In children with T21-associated IESS, a large Irish cohort reported spasm cessation in 60% of children treated initially with prednisolone compared with 28% treated with vigabatrin [18]. Other retrospective cohorts have similarly reported higher response rates with ACTH or corticosteroids than with vigabatrin [13,17].

Individual reports have also described responses to vigabatrin in children with T21-associated IESS. In a prospective study, without a control group, Nabbout et al., 4 of 5 children with T21 and IESS responded to vigabatrin, with spasm cessation within 2 weeks [6]. These findings reinforce that vigabatrin remains an important first-line treatment option, although the small sample size limits conclusions regarding its comparative efficacy. A review of published retrospective T21-associated IESS cases reported an overall response rate of 86% among 141 children treated with steroids (ACTH or corticosteroids) and 76% among 37 children treated with vigabatrin, with reported relapse rates of 16% and 9%, respectively [2,5,9–17,19].

However, these figures represent descriptive summaries of individual published heterogeneous studies rather than formal pooled estimates or meta-analytic results. These studies differed in treatment regimens, doses, EEG criteria, definitions of response, and follow-up, limiting direct comparison across studies.

Prospective data provide additional context. In the National Infantile Spasms Consortium cohort, hypsarrhythmia resolution at 3 months occurred in 74% of children with T21 treated with ACTH and 83% treated with corticosteroids, compared with 20% of those treated with vigabatrin; however, only five children received vigabatrin, precluding a reliable comparison [20]. The International Collaborative Infantile Spasms Study (ICISS) demonstrated that adding vigabatrin to hormonal therapy improved early cessation of infantile spasms compared with hormonal therapy alone in the overall study population [11,21]. However, the T21 subgroup did not demonstrate a clear additional benefit from combination therapy, although this analysis was limited by its small sample size and should be interpreted cautiously [11].

Cao et al. provide the largest published direct comparison of first-line hormonal therapy and vigabatrin in children with T21-associated IESS. In the multicenter retrospective cohort of 114 children, 85.5% ultimately achieved IESS remission during follow-up, regardless of whether remission occurred with first-line monotherapy or required subsequent treatment. Among children who achieved remission with first-line monotherapy, 17 of 54 (31.5%) receiving hormonal therapy achieved remission without subsequent relapse, compared with 6 of 36 (16.7%) receiving vigabatrin ($P = 0.114$). Multivariable regression analysis was used for key outcomes, including time to remission, and included initial treatment for IESS, treatment lag, age at IESS onset, and sex. There was an association with shorter median time to remission with first-line hormonal monotherapy than with vigabatrin (41 days [IQR 18.5–102] vs 142 days [IQR 66–285], respectively; $P < 0.001$) [8]. However, important limitations of Cao et al.'s findings include the retrospective design, lack of comprehensive measures of baseline disease severity, the potential influence of subsequent treatments after first-line therapy, and variability in center-specific treatment practices. Taken together, the available evidence in the literature supports the efficacy of hormonal therapy and vigabatrin as first-line treatment options for T21-associated IESS. Hormonal therapy may be associated with more rapid remission, but the comparative effectiveness of these treatments remains uncertain due to limitations with study methodology.

Relapse

Relapse, defined by Cao et al. as recurrence of epileptic spasms after at least 28 days of seizure freedom, confirmed

clinically and by EEG, remains an important concern after successful treatment of IESS. In their retrospective cohort, 25% of children experienced at least one relapse and 2% experienced a second relapse. Relapse rates did not differ significantly according to first-line treatment with hormonal therapy or vigabatrin [8]. These findings are consistent with prospective data from Chen et al., which also found no difference in relapse rates according to initial therapy among children who achieved early IESS cessation [20]. However, differences in treatment protocols, follow-up, and relapse definitions across studies limit direct comparisons, and further prospective data are needed to determine whether treatment choice influences long-term relapse risk.

However, other retrospective studies have suggested that relapse may be more frequent following first-line vigabatrin therapy. In one cohort of children initially treated with vigabatrin, those with T21 had higher relapse rates compared with children with no identified etiology (42% vs. 10%), with relapse occurring at a median of approximately eight months after seizure cessation [19]. In contrast, a similarly designed study of children with T21 treated with hormonal therapy did not demonstrate an increased relapse risk compared with a comparable control group, suggesting that relapse patterns may differ depending on the initial treatment strategy and underlying etiology [15]. Relapse may also occur much later; in an early ACTH-treated cohort, 4 of 7 initial responders (57%) relapsed, with some relapses occurring up to two years after treatment cessation [16]. Similarly, longer follow-up in the Cao et al. cohort identified relapses up to 18 months after treatment, including recurrent relapses in some children [8]. These findings highlight the need for prolonged surveillance after IESS remission and continued investigation into factors that predict relapse, particularly given the association between relapse and subsequent epilepsy risk. Again, these findings should be interpreted with caution, given substantial methodological differences among the studies.

Treatment Lag

Delayed diagnosis remains common in the T21 population. The early signs of infantile spasms can be subtle and easily overlooked, particularly in infants who already show developmental differences, and the resulting delay in treatment is a persistent challenge [22,23]. Greater education of families and clinicians about how IESS presents may help shorten this lag, though the effect of timing on outcome in T21 has been inconsistent across studies. Cao et al. reported a median treatment lag of 1 month (range 0–15 months) from observed onset of infantile spasms to treatment. In adjusted analyses, each additional month of treatment lag was associated with higher odds of subsequent LGS (OR 1.34, 95% CI 1.00–1.78) and ASD (OR 1.51, 95% CI 1.19–2.05) [8]. These findings should be interpreted as observational associations

rather than causal effects. Treatment lag may be influenced by caregiver recognition of spasms, including potentially subtle or unrecognized early events, as well as underlying disease characteristics not fully captured in the retrospective study.

Eisermann et al. similarly found that a delay of more than 60 days was associated with poorer outcomes, including longer IESS duration, worse developmental outcomes, higher epilepsy risk, and higher rates of ASD [5]. Conversely, Harvey et al. found no significant association between treatment delay beyond 60 days and either IESS cessation or ongoing seizures [18]. In the National Infantile Spasms Consortium data, children treated with ACTH had longer treatment lags, although not significantly so, yet had the highest response rate among standard therapies [20]. Together, these findings highlight the complexity of the relationship between treatment timing and outcomes in T21-associated IESS and the potential for residual confounding and reverse causation; they do not establish that treatment delay independently causes LGS or ASD.

Treatment Safety and Risk–Benefit Considerations

Treatment efficacy must be balanced against potential adverse effects. Hormonal therapy can cause hypertension, hyperglycemia and other metabolic complications, infection risk, and behavioral or gastrointestinal effects, whereas vigabatrin carries a risk of retinal toxicity and can be associated with reversible MRI signal abnormalities in infants and young children [24–26]. Cao et al. did not systematically collect or compare treatment-related adverse events, and therefore their study cannot inform the comparative safety of these therapies [8]. In clinical practice, treatment selection should incorporate these potential risks alongside the urgency of achieving rapid seizure control, with decisions individualized through discussion between clinicians and families.

Long-Term Outcomes

Children with T21 and IESS are generally thought to have better long-term outcomes than those with IESS of unknown etiology, but families should still be counseled about the risk of later epilepsy [5]. Cao et al. found this risk to be 31%, similar to the 25% reported in another large cohort [18,27–29]; prior studies have reported rates of ongoing seizures ranging from 30% [4]. With a median follow-up of 25 months from IESS onset to last neurology visit (range 0.5–246), the Cao et al. cohort was followed longer than many prior series, better capturing this long-term risk. As with relapse, the choice of hormonal therapy versus vigabatrin as first-line treatment in their study did not predict which children went on to develop epilepsy [8].

Progression to Lennox–Gastaut syndrome (LGS) has been documented only infrequently in T21 relative to other causes

of IESS [30,31]. Cao et al. found that first-line hormonal therapy versus vigabatrin likewise did not predict ongoing epilepsy, though a history of relapse did increase the odds of subsequent epilepsy, drug-resistant epilepsy, and LGS [8]. One review spanning five epilepsy centers over 30 years identified just 13 children with T21 and LGS, and in none of these cases did IESS precede the onset of LGS. Reports of LGS following IESS in T21 therefore remain rare [10,14,31]; in one such series, all four children who developed LGS had received nonstandard therapies for their spasms IESS [14].

A quarter of the children in Cao's cohort developed autism spectrum disorder (ASD), again with no difference by first-line treatment. Some studies, as Cao et al., have found an association between longer treatment lag and ASD [5,9,16], though others have not [18], possibly reflecting differences in methodology and follow-up duration across cohorts. Developmental delay frequently accompanies IESS, but many studies show that it often improves or resolves after spasms are controlled [2,6,22,28]. However, most studies have not included formal neuropsychological evaluations to properly document neurodevelopment over time.

While the available evidence generally favors hormonal therapy as first-line treatment for T21-associated IESS, several limitations preclude a definitive comparison between strategies. Differences in study design, treatment regimen, dosing protocol, and outcome definition, including EEG data, all contribute to substantial heterogeneity across the published literature; remission, relapse, and clinical versus electroclinical response have all been defined inconsistently, complicating direct comparison. Follow-up is also frequently limited to the short term, which risks overlooking later epilepsy, ASD, developmental outcomes, or delayed relapse. Even the largest prospective consortium study included only five vigabatrin-treated children, substantially limiting its power to compare the two treatments directly [20].

Patient populations also differ meaningfully across studies. Some cohorts, including that of Cao et al., focused on children with IESS in the absence of structural brain abnormality, while others included children with abnormal neuroimaging, such as perinatal stroke or other acquired brain injury, that may independently shape treatment response and long-term outcome. Hormonal therapy itself is also not a uniform intervention: ACTH dosing has varied considerably between studies. The conflicting findings across the literature, then, likely reflect differences in patient selection, treatment protocol, and study methodology as much as any true difference in efficacy between agents. Larger prospective studies with standardized treatment protocols, consistent definitions of electroclinical remission, predefined EEG assessment, comprehensive neurodevelopmental follow-up, and adequate representation of both hormonal- and vigabatrin-treated children are needed to settle the question of optimal first-line treatment.

Clinical Vignette

A 2-year-old boy with trisomy 21, confirmed after birth via genetic testing, following prenatal identification of a ventricular septal defect, developed infantile spasms at 7 months of age. Within days, his family noted developmental regression, including reduced smiling, hypotonia, and loss of previously acquired head control. EEG obtained 5 days after the onset of observed epileptic spasms demonstrated hypsarrhythmia, confirming the diagnosis of IESS, and treatment was initiated promptly. Brain MRI obtained 2 months after spasm onset was normal.

Vigabatrin was initiated first at 100 mg/kg/day and increased to 200 mg/kg/day because of ongoing spasms. It was continued for 6 months without electroclinical response. Ophthalmologic examinations were performed during treatment. Oral prednisone (6 mg/kg/day for 2 weeks followed by a 2-week taper) was subsequently given at 8 months and again at 11 months due to persistent epileptic spasms. Steroid monitoring included periodic blood pressure, urine glucose, and fecal occult blood testing; irritability occurred during steroid treatment. Valproic acid (maximum 40 mg/kg/day) was initiated at 9 months and continued, with normal serial CBC and liver function testing. At 12 months, a 4:1 ketogenic diet was initiated and was well tolerated, but was discontinued after 6 months because of lack of efficacy. Beta hydroxybutyrate levels ranged from 2 to 3 mm/L. Topiramate (7 mg/kg/day) was subsequently trialed but discontinued after 1 month because of a rash. At 2 years of age, clobazam (1.5 mg/kg/day) was added following the emergence of drop seizures.

Despite early recognition and sequential treatment with standard therapies, hypsarrhythmia never resolved and epileptic spasms persisted, with seizures associated with electrodecremental responses. The most recent EEG demonstrated slow spike-and-wave activity and paroxysmal fast activity during sleep, and ongoing epileptic spasms as well as tonic seizures, consistent with evolution to Lennox-Gastaut syndrome [32]. At 2 years, he had significant developmental impairment, with slow developmental progress, sitting only with support and no expressive language.

This case illustrates that prompt recognition and treatment of IESS do not guarantee electroclinical remission or prevent progression to drug-resistant epilepsy, particularly in the context of T21. It also highlights the complexity of treatment decisions when first-line and subsequent therapies fail. Importantly, this single case is illustrative and cannot be used to infer comparative treatment efficacy or outcomes.

Beyond First-Line Treatment: Possible Biological Contributors

The vignette and the variable outcomes observed in

T21-associated IESS suggest that factors beyond the choice and timing of first-line therapy may contribute to treatment response and long-term neurological outcomes. In most children, IESS is thought to reflect intrinsic genetic mechanisms, although acquired brain injury may contribute to a minority of cases [33–35]. One proposed mechanism involves overexpression of *KCNJ6*, which encodes the GIRK2 potassium channel and may contribute to excitation–inhibition imbalance in T21-associated infantile spasms [36].

The additional copy of chromosome 21 alone is unlikely to explain the marked clinical heterogeneity of T21. Studies of partial duplications and deletions suggest complex genotype–phenotype relationships, with multiple chromosomal regions contributing to different clinical features [37,38]. Studies of congenital heart disease in T21 have similarly identified candidate susceptibility regions [39]. Although these findings do not establish genetic modifiers of IESS, they provide a hypothesis-generating framework for investigating whether genomic variation beyond trisomy 21 contributes to susceptibility, treatment response, or progression to drug-resistant epilepsy. Epigenetic studies in T21-associated leukemia further illustrate biological heterogeneity despite a shared trisomy 21, although these findings cannot be directly extrapolated to epilepsy [40].

No validated biomarkers currently identify children with T21 who will develop IESS or progress to drug-resistant epilepsy. Candidate biomarkers under investigation in IESS more broadly, including quantitative and network-based EEG measures [41,42] and MRI measures of brain connectivity [43], warrant evaluation in T21. Future studies integrating clinical, genomic, EEG, and neuroimaging data may help identify markers of disease susceptibility and treatment response and ultimately support more individualized care.

Conclusion

Does the choice of first-line therapy influence outcomes in T21-associated IESS? The multicenter study by Cao et al. provides the largest comparative cohort to date of children with T21-associated IESS treated with hormonal therapy or vigabatrin [8]. They found that hormonal therapy was associated with a higher likelihood of electroclinical remission and a shorter time to remission, consistent with previous reports. However, current evidence does not demonstrate that first-line treatment choice alone determines long-term outcomes, including ongoing epilepsy, evolution to LGS, or ASD.

Heterogeneity across studies likely reflects variation in methodology, treatment protocols, and outcome definitions, but they may also point to a broader concept: outcomes in T21-associated IESS are influenced by factors beyond the

initial therapeutic choice. The accompanying clinical vignette illustrates that even with early recognition, minimal treatment delay, and appropriate escalation of therapy, some children progress to refractory epilepsy, highlighting the contribution of underlying biological factors intrinsic to T21.

Future research should extend beyond treatment comparisons to better define the genetic, epigenetic, and molecular mechanisms that influence susceptibility to IESS, treatment response, and long-term outcomes in T21. Such advances will improve prognostic counseling, enable early risk stratification, and support the development of more personalized therapeutic strategies for children with T21-associated IESS.

Research Ethics and Patient Consent

The patient provided consent to publish the clinical vignette in this manuscript.

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