Drug resistant epilepsies: a multicentre case series of steroid therapy

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HIGHLIGHTS

- Drug-resistant epilepsies (DRE) are a challenge for paediatricians.
- The steroid must be considered a therapeutic option in these forms of epilepsy.
- 62.68% of patients presented a reduction in epileptic seizures greater than 50%.
- DREs with structural and immune aetiology respond better than genetic forms.
- The most effective steroid protocol is methylprednisolone 30 mg/kg/day for 3 days.

Drug resistant epilepsies: a multicentre case series of steroid therapy

Raffaele Falsaperla[1,2] CA, Ausilia Desiree Collotta[1,3] CA, Simona D. Marino[1] , Vincenzo Sortino[1,3], Roberta Leonardi[3], Grete Francesca Privitera[4], Alfredo Pulvirenti[4], Agnese Suppiej[5], Marilena Vecchi[6], Alberto Verrotti[7], Giovanni Farello[7], Alberto Spalice[8], Maurizio Elia[9], Orazio Spitaleri[10], Marco Micale[11], Janette Mailo[12], Martino Ruggieri[13],

1 Paediatric and Paediatric Emergency Department, University Hospital "Policlinico-San Marco," Catania, Italy.

2Unit of Intensive Care and Neonatology, University Hospital "Policlinico-San Marco" Catania, Italy.

3Postgraduate Training Program in Pediatrics, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

4 Department of Clinical and Experimental Medicine, University of Catania, c/o Dept. of Math. and Comp. Science Viale A. Doria, 6, 95125, Catania, Italy.

5 Maternal and Child Department, Ferrara University Hospital; Medical Science Department (D.O.), Ferrara University

6 Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, Padova University Hospital, Padova, Italy.

7 Clinical Paediatric, University of Perugia, Hospital SM della Misericordia, Perugia, Italy

8 Department of Paediatrics, Child Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy.

9 Unit of Neurology and Clinical Neurophysiopathology, Oasi Research Institute, IRCCS, Troina, Italy.

10 Paediatric Neuropsychiatry Unit , Hospital " S.Marta e S.Venera", Acireale, Italy

11 Paediatric Neuropsychiatry Unit, Maternal and Child Department, Arnas Civico, Palermo, Italy.

12 Division of Paediatric Neurology, University of Alberta, Canada

13 Unit of Clinical Pediatrics, Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, University of Catania, 95124 Catania, Italy

Corresponding Authors

Raffaele Falsaperla

raffaelefalsaperla@hotmail.com

Ausilia Desiree Collotta

ausilia.collotta.92@gmail.com

Abstract

Purpose: Our study aimed to evaluate the effectiveness of corticosteroids on seizure control in drug-resistant epilepsies (DREs). Our primary goal was to assess the response to steroids for various underlying etiologies, interictal electroencephalographic (EEG) patterns and electroclinical seizure descriptions. Our second goal was to compare steroid responsiveness to different treatment protocols.

Methods: This is a retrospective multicentre cohort study conducted according to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology). The following data were collected for each patient: epilepsy etiology, interictal EEG pattern, seizure types and type of steroid treatment protocol administered.

Results: Thirty patients with DRE were included in the study. After 6 months of therapy, 62.7% of patients experienced reduced seizure frequency by 50%, and 6.6% of patients experienced complete seizure cessation. Findings associated with favourable response to steroids included structural/lesional etiology of epilepsy, immune/infectious etiology and focal interictal abnormalities on EEG. Comparing four different steroid treatment protocols, the most effective for seizure control was treatment with methylprednisolone at the dose of 30 mg/kg/day administered for 3 days, leading to greater than 50% seizure reduction at 6 months in 85.7% of patients. Treatment with dexamethasone 6 mg/day for 5 days decreased seizure frequency in 71.4% of patients. Hydrocortisone 10 mg/kg administered for 3 months showed a good response to treatment in 71%.

Conclusions: In our study, two-thirds of patients with DRE experienced a significant seizure reduction following treatment with steroids. We suggest considering steroids as a potential therapeutic option in children with epilepsy not responding to conventional antiseizure medicines (ASM)**.**

KEYWORDS: drug-resistant epilepsies; steroid-therapy; neuroinflammation.

1. Introduction

According to the International League Against Epilepsy (ILAE), drug-resistant epilepsies (DRE) are defined as epilepsies resistant to two or more antiseizure medicines (ASM), appropriately chosen and used whether as monotherapies or in combination [1]. DRE is a challenging condition that affects approximately 10-20% of all children with epilepsy [2-6.]. According to other studies this percentage even rises to 30-40% [7-10].

It is associated with significant morbidity due to the high seizure burden and multiple medications used. Recent studies have shown that neuroinflammation may both precipitate and sustain seizures, implying that inflammation may be involved not only in epileptogenesis but also in the development of the drug-resistant profile. Due to their role in immunomodulation and immunosuppression, steroids have been considered potential candidates in the ongoing search for novel anti-epileptic therapies [11]. The mechanism of action of steroids is thought to be interference with the inflammatory cascade, believed to trigger ongoing seizures [12-15]. With this hypothesis in mind, several different treatment protocols have been used in studies with the goal

of breaking the seizure refractoriness. Evidence supports the use of corticosteroids as treatment for epileptic spasms; however, there are still few studies on their effect on epileptic encephalopathy or drug-resistant epilepsies [16]. The objectives of this study were twofold: first, to evaluate the efficacy of steroids in DRE in children, particularly focusing on aetiology, interictal EEG and seizure types and second, to assess the effectiveness of the steroid treatment protocols used by comparing steroid types.

2. Materials and methods

This retrospective multi-centre cohort study included all DRE patients treated with steroids in paediatric neurology centres of Catania, Padova, Chieti, Troina, Palermo and Rome between 2015-2017. This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, all points on the checklist have been respected.

2.1 Eligibility criteria

Children with DRE and meeting the following criteria were included:

1) Diagnosis of DRE according to the classification of the ILAE [1].
2) Treatment with steroids as an add-on agent to the other ASM (reason 1).
3) Treatment with at least two ASMs for a minimum of 4 months (reason 3).
4) No change in ASM was found for at least 8 weeks immediately before inclusion in our study and also during treatment and during follow-up (reason 4).

The exclusion criteria were:

1) Patients under 6 months and over 14 years of age (reason 2).
2) Patients diagnosed with any of the following: infantile spasms syndrome, syndrome of electrical status epilepticus during use spike-wave activation in sleep (SWAS), or Landau-Kleffner syndrome (LKS) (reason 5).
3) Patients with a history of malignancy within the past 3 years prior to randomization (reason 6).
4) Patients with moderate to severe hepatic and/or renal impairment (reason 7).
5) Patients with any severe and/or uncontrolled medical conditions at randomization, such as symptomatic congestive heart failure, congenital heart diseases, or any other clinically significant cardiac disease, or significant symptomatic deterioration of lung function (reason 8).
6) Patient with uncontrolled diabetes or with uncontrolled hyperlipidemia (reason 9).
7) Patients with a history of organ transplant (reason 10).

8) Patients receiving any anti-cancer therapies or who have received anti-cancer therapy within 4 weeks of study entry, including chemotherapy, radiation therapy, and antibody-based therapy (reason 11).

9) Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent at study entry (reason 12).

2.3 Collected Data

All the authors accurately reviewed the medical records of each patient selected on the basis of the inclusion and exclusion criteria (R.F., A.D.C., S.D.M. and V.S. for Catania; M.V. for Padua; A. V. and G.F. for Chieti; E.M. for Troina ; M.M. for Palermo and A.S. for Rome), the data were extrapolated and discussed within the group.

Written informed consent was obtained from the children's parents or legal guardians.

For each individual patient selected on the basis of the inclusion and exclusion criteria, all data were collected by the doctors of each centre (R.F., A.D.C., S.D.M. and V.S. for Catania; M.V. for Padua; A. V. and G.F. for Chieti; E.M. for Troina ; M.M. for Palermo and A.S. for Rome).

The following data were collected for all study participants: gender, epilepsy aetiology, age at epilepsy onset, seizure type, seizure frequency, interictal video-EEG in wakefulness and sleep, age at treatment initiation, antiepileptic drugs tried, steroid type, steroid treatment dose, duration of steroid therapy, the effect of steroid therapy on seizure frequency and EEG (tables 1 and 2).

Each patient was assigned a random number from 1 to 30 to avoid the names' initials and ensure anonymity.

The patients were classified by the authors of the paper (R. F., A.D.C. and R.L.) into groups based on the following data:

1) Aetiology: in "Structural", "Genetic" and "Immune/Infectious", according to ILAE guidelines [17]

2) interictal EEG: "focal", "multifocal" and "generalised";

3) seizure types: "Generalised Tonic Seizures", "Generalised Tonic-Clonic Seizures", "Focal Tonic Seizures", "Focal Clonic Seizures", "Focal Onset Generalised Tonic Seizures", according to the classification of ILAE [18-20];

4) type of steroid protocol administered.

For each of these classes, we analysed four different temporal instants before ("before therapy" denoted T0) and after the end of therapy ("2 weeks" denoted T15, "1 month" denoted T30 and "6 months denoted T180").

For each patient, we scored the number of daily crises to be able to compare the different times examined.

2.4 EEG

The patients underwent an EEG with synchronised video (video-EEG) [21,22].

Three authors (R.F., C.A.D., and S.D.M) independently evaluated each video-EEG that was compared with the EEG of the same patient performed at a different time (T0, T15, T30, T180).

Fleiss' kappa (K) [23] was used to assess agreement among raters in the electroencephalographic interpretation. An online calculator (dfreelon.org) was used to calculate K. Landis and Koch [24] interpreted the K as follows: <0: low agreement, 0.01–0.2: slight agreement, 0.21–0.4: fair agreement, 0.41–0.6: moderate agreement, 0.61–0.8: substantial agreement, and 0.81–1: nearly perfect agreement.

The protocol we used follows the recommendations of the ILAE and the International Federation of Clinical Neurophysiology [25, 26]. We used head caps with prewired electrodes located according to the full 10–20 pad placement system [27].

We used one electrocardiography (ECG) channel and two electromyography (EMG) channels [25, 26]. The electrode impedances were 5-10 kΩ. A camera recorded all the patient's movements [25, 26].

A 20-30-minute awake recording was used as baseline and it was followed for 5-10 minutes by activation procedures (eye opening and closure, hyperventilation, and intermittent photic stimulation) [25, 26, 28, 29]. Then the patients were asked to go to sleep. According to the recommendations of the ILAE and the International Federation of Clinical Neurophysiology [25, 26], patients underwent partial sleep deprivation or the administration of melatonin (1–3 mg administered 30–60 min before EEG recording) if it was not possible to deprive them. Children younger than 6 years shortened their sleep by 1–3 hours or by an amount deemed necessary to fall asleep at the time of the EEG. Children aged 6 to 12 years went to sleep 2 hours later than usual and woke up 2 hours earlier than usual, remaining awake until the EEG. Children older than 12 years went to sleep 2 hours later than usual, but at the latest at 00 a.m. Stay awake from 4 a.m. until the EEG.

2.5 Drug dosage and assessment of response

Each centre administered the steroid protocol validated by its own hospital to its patients. From our retrospective collection, the following steroid therapy protocols emerged:

1. Intravenous methylprednisolone high dose: 30 mg/kg/day for 3 days (Protocol 1, P1), followed by tapering with oral prednisolone 1.2 mg/kg/day for 4 weeks [30]
2. Intravenous methylprednisolone low dose: 15 mg/kg/day for 5 days, followed by tapering with oral prednisolone 1.2 mg/kg/day for 4 weeks (P2) [31]
3. Oral hydrocortisone: 10mg/kg per day for 1 month, 5 mg/kg per day for 1 month, 2.5 mg/kg per day for 1 month, 1 mg/kg per day for 1 month, and 1 mg/kg on alternate days for 2 months. (P3) [32]

4. Intravenous dexamethasone: 6 mg/Kg per day for 5 days, 5 mg/kg per day for 2 days and 2 mg/kg for 2 days (P4) [33]

Follow-up was performed by a paediatric neurologist (R.F., M. S. and C.A.D.) who documented the therapeutic response. The response to steroid treatment was based on seizure diaries filled out by the patients' parents. Seizure diaries included seizure characteristics, frequency, intensity, and duration, similarly to the study performed by Fisher et al. [34].

Every day, the parents report the number of seizures starting four weeks before therapy and stopping six months after the end of therapy. To compute the number of seizures before therapy for each patient, we calculated the mean of the seizures per day in the four weeks preceding therapy. After the therapy was administered, we calculated an average mean, giving the days a higher weight as the deadline approached. For instance, for T30, the day thirty after therapy of the one-month deadline had a higher weight compared to the day two after therapy.

2.6 Statistical analysis

Statistical analysis has been performed using R (v.4.3.0). First, we tested the population distribution using a Shapiro-Wilk test. Successively, Kruskal-Wallis nonparametric one-way analysis of variance has been used to examine the changes in seizure frequency at "before therapy, at 2 weeks, at 1 month and at 6 months" considering several variables. Moreover, the Wilcoxon test has been employed to compare the intragroup differences at the four observation times (T0, T15, T30, and T180). A p value < 0.05 was considered significant.

2.7 Endpoint

The primary endpoint was to quantify the reduction of seizures in relation to steroid therapy in the follow-up period (T0, T15, T30, T180).

We defined "complete responders" as those patients who were seizure-free (complete cessation of seizures), considering the observation time from the day they finished steroid therapy until the 15th day for T15, the 30th day for T30 and the 180th day for T180. The average was calculated by giving the days a greater weight as the deadline approached.

All patients who experienced greater a seizure reduction than 50% were considered partial responders. On the other hand, less than a 50% reduction or no change (0%) or increase in seizures were considered non-responders.

The secondary endpoint focused on factors that predispose to a better or worse response to steroid treatment (based on the type of aetiology, electroclinical presentation and interictal EEG).

The tertiary and final endpoint was to evaluate the response to the four different protocols.

3. Results

Our database search found 59 patients with a diagnosis of DRE, according to the standard international criteria [1]. Applying the inclusion and exclusion criteria, we collected 30 patients (Figure 1).

3.1 Demographic Data

Of the 30 patients included in the study, 16 were males and 14 were females (table 1). The age of seizure onset ranged from 0 months to 118 months (9 years 10 months), with a mean of 32.7 months (approximately 2 years 10 months). The starting age of steroid treatment ranges from 5 years to 11 years and 11 months, with an average of 77.2 months (about 6 years and 4 months) (table 2).

3.2 Response to the treatment in all patients

In all 30 patients receiving steroid therapy, regardless of treatment protocol, a complete response occurred in only one patient (patient number 29) at 15 days and 1 month of therapy and in two patients (patient numbers 14 and 29) at 6 months of therapy (table 2).

Patient number 14 at 2 weeks and 1 month had a 50% reduction in seizures per day.

Overall, we achieved complete response and partial response (> 50% seizure reduction) in 16.6% (5/30) at 15 days and in 30% (9/30) after 1 month of treatment. The greatest reduction occurred in the 6 months following treatment equal to 62.7%. Therefore, compared to the reduction obtained 15 days after the therapy, the reduction at 6 months was 35% more and compared to 30 days the reduction was 29.4% more.

The non-responders, on the other hand, were 83.3% after 15 days of therapy and 70% after 1 month of therapy, which dropped to 36.6% after six months of therapy.

After six months of therapy, among the patients considered non-responders (11 patients) we have: 4 patients (patients numbers 6, 9, 22 and 26) who presented a 50% seizure reduction, 2 patients who did not respond to therapy (patients numbers 8 and 11) and in only one case we had an increase in seizures (patient number 17).

3.3 Response to treatment according to aetiology of seizures

The aetiologies were as follows (table 1):

A. structural abnormalities (50% of cases, 15 patients): hippocampal sclerosis (3 of 15 patients), polymicrogyria (2 of 15 patients), perinatal ischemic infarct (3 of 15 patients), cortical dysplasia (4 of 15 patients), hypothalamic hamartoma (1 of 15 patients), punctate white matter lesions (1 of 15 patients), injury to cerebrocortical-deep nuclear and perirolandic cortex (1 of 15 patients).

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Conflict of Interest
The authors declare that they have no competing interests.