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Original article

Treatment of infantile spasms by pediatric neurologists in Japan

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Abstract

Objective: To clarify changes in clinical practice for infantile spasms, including West syndrome, in Japan over the past two decades.

Methods: We investigated common treatment strategies for infantile spasms among 157 pediatric neurologists from a designated training facility for pediatric neurology and/or a designated training facility for epilepsy in Japan. A questionnaire was used to investigate use of adrenocorticotropic hormone (ACTH) therapy including daily dose, treatment duration, and tapering off period, and preferred first to fifth-line treatment choices.

Results: Among 119 responses (75.8%), 107 enabled analysis of ACTH therapy and 112 were used to determine preferred order of first to fifth-line treatments. Over 80% respondents reported an initial ACTH dose of ≤0.0125 mg/kg/day, with a treatment duration of 14 days and various tapering periods. Following an unfavorable response of seizures to ACTH, 80% respondents increased the dose and/or extended treatment duration. The same ACTH therapy regimen was performed for symptomatic and cryptogenic patients at 95 facilities (88.8%). Preferred orders of therapeutic agents were the same for both symptomatic and cryptogenic patients at 64 facilities (57.1%). Over half the respondents selected vitamin B6 or valproate as the first and second-line treatments instead of ACTH therapy, while ACTH therapy was the most frequently selected third-line treatment.

Conclusions: Current ACTH therapy regimens have lower doses and shorter durations than previously reported. However, treatment strategies for infantile spasms have not changed much in two decades. ACTH therapy should be the first/second-line treatment rather than third-line or later, especially for cryptogenic infantile spasms.

Keywords: Adrenocorticotropic hormone; Epilepsy; Epileptic spasms; Valproate; Vigabatrin; Vitamin B6; West syndrome

1. Introduction

Adrenocorticotropic hormone (ACTH) therapy has been established as the primary treatment for infantile spasms, including West syndrome. Guidelines from the Japan Epilepsy Society emphasize ACTH therapy as the most effective treatment for infantile spasms. Furthermore, they highlight the importance of implementing ACTH therapy as early as possible, especially in patients with cryptogenic etiology, to improve long-term developmental outcomes [1]. A recent systematic review [2], US guidelines [3], and recommendations from the International League Against Epilepsy [4] all

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highlight ACTH therapy as the preferred initial therapeutic choice for infantile spasms. Moreover, they add that low-dose ACTH is probably as effective as high-dose ACTH, and that both dosages may be preferable than other treatments to improve long-term neurodevelopmental outcomes.

However, there are several different ACTH preparations used in different countries. Cortrosyn Z® intramuscular injection (Daiichi Sankyo Company Ltd.) is a synthetic analogue of ACTH (tetracosactide acetate) used for ACTH therapy in Japan, where natural ACTH is not commercially available. Cortrosyn Z® is a zinc hydroxide suspension of a 24-amino-acid polypeptide, and 1 mg of synthetic ACTH is considered to be equivalent to 40 IU of natural ACTH.

Synthetic ACTH is associated with more adverse effects and is speculated to have stronger effects on seizure activity than natural ACTH [5]. This is also observed with Synacthen Depot®, which is a different preparation and concentration of tetracosactide acetate. Adverse effects associated with ACTH therapy have led to hesitation in implementing the treatment among physicians in Japan. Such adverse effects include immunosuppression, hypertension, brain shrinkage, irritability, obesity, and electrolyte imbalance. Immunosuppression may cause serious infection, which is the most common cause of death during ACTH therapy [6]. Moreover, subdural hemorrhage can occur in association with brain shrinkage and rupture of bridging veins [7].

The risk of adverse effects in ACTH therapy appears to depend on the dose and duration of therapy. As a result, many Japanese clinicians use reduced doses and durations for ACTH therapy [5,8,9]. Indeed, guidelines from the Japan Epilepsy Society recommend lower doses and as short a duration as possible for ACTH therapy [1]. Furthermore, the guidelines recommend that ACTH therapy should be performed as soon as possible, within a month of onset, especially among patients with non-symptomatic (i.e., cryptogenic) etiology [1].

Previous surveys of treatments for infantile spasms conducted over 10 years ago reported that many Japanese pediatric neurologists considered ACTH therapy as a third or fourth-line treatment, behind vitamin B6, valproate, and/or zonisamide [10–12]. This tendency appears to be due to a desire to avoid the serious adverse effects of ACTH therapy, and/or the necessity for admission for ACTH therapy. However, recent reviews suggest that there is insufficient evidence for the effectiveness of agents and combination therapies, other than hormonal therapy (ACTH and oral steroids) and vigabatrin, in the short-term treatment of infantile spasms [2–4]. Moreover, delaying ACTH therapy might reduce or miss the chance for better long-term outcomes for the patient.

Therefore, we conducted a survey of pediatric neurologists to clarify changes in clinical practice for the treatment of infantile spasms in the past two decades in Japan. Our results may provide an outline of treatment strategies that can be further explored in future clinical trials of infantile spasms, including West syndrome.

2. Materials and methods

We conducted a descriptive study to survey preferred treatment strategies for infantile spasms among Japanese pediatric neurologists. We prepared a questionnaire which included a maximum of 30 questions. The questions aimed to assess current practice of ACTH therapy and differences in early treatment strategies corresponding to the etiology of patients.

Questions probed the following: (1) daily dose, treatment duration, and tapering off period of ACTH therapy, changes to ACTH dose and/or extension of treatment duration following an unfavorable seizure response, and repeated ACTH therapy following relapse of seizures within a year, for patients with cryptogenic or symptomatic etiologies; (2) whether the same ACTH therapy regimen is used for symptomatic and cryptogenic patients, and situations in which ACTH therapy for symptomatic patients is not the same as for cryptogenic patients; (3) preferred order of treatments from first-line to fifth-line among ACTH therapy, vitamin B6, valproate, zonisamide, clobazam, clonazepam, topiramate, lamotrigine, intravenous immunoglobulin therapy, thyrotropin releasing hormone therapy, ketogenic diet, prednisolone, surgical treatments and others for each etiology, cryptogenic or symptomatic (and specifically for subgroups of patients with focal cortical dysplasia or hemimegalencephaly, and tuberous sclerosis).

In June 2014, we sent the questionnaire to 157 heads of a designated training facility for pediatric neurology and a pediatric department at a designated training facility for epilepsy in Japan.

The study was approved by the Saitama Children's Medical Center Institutional Review Board.

3. Results

3.1. Sample

In total, we obtained 119 responses (75.8%) from designated training facilities in Hokkaido (replied/sent: 7/8), Tohoku (5/8), Kanto (37/52), Chubu (21/29), Kinki (23/28), Chugoku (8/9), Shikoku (3/6), and Kyusyu (15/17). Among the responses, 12 facilities reported that they did not perform ACTH therapy (patients were referred to another institute for the therapy), and therefore data regarding ACTH therapy was analyzed from a final sample of 107 facilities. We obtained 112 responses regarding the preferred order of early treatments for

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