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Retreatment with intravenous immunoglobulin (IVIG) of refractory Guillain-Barre syndrome in children

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RESUMEN

El síndrome de Guillain-Barré (SGB) es una polineuropatía aguda mediada por autoinmunidad precedido de una infección [1]. Uno de los tratamientos preferidos es la plasmaféresis y la administración de gammaglobulina intravenosa (IVIG por sus siglas en inglés), usualmente 2 g/kg administrado en uno o dos días. La falla al tratamiento es infrecuente, en contraste con otras alteraciones inmunológicas como la enfermedad de Kawasaki, en la cual el retratamiento con IVIG está bien descrito. Informamos el caso de una niña con SGB quien no obtuvo respuesta satisfactoria con el esquema habitual de IVIG. En adultos con SGB el retratamiento con IVIG es poco frecuente [2,3]. Hasta donde sabemos, no hay publicaciones previas de retratamiento con IVIG en niños con SGB.

Palabras clave: Síndrome de Guillain-Barre, inmunoglobulina, polineuropatía, autoinmunidad.

ABSTRACT

Guillain-Barré syndrome (GBS) is an acute symmetrical paralyzing disease due to a demyelinating polyrradiculoneuropathy, often induced by a preceding infection [1]. The main modalities for the treatment of GBS include plasmapheresis and intravenous immune globulin. Reports of the use of IVIG in children with GBS are limited: 1 g/kg for two days or 400 mg/kg for five days. While these studies in children are not definitive because of design limitations, their results are consistent with the larger randomized trials in adults [2,3].

Key words: Guillain-Barré syndrome, immunoglobulin, polyneuropathy, autoimmunity.

Abbrevations: GBS, Guillain-Barré Syndrome; IVIG, intravenous immunoglobulin; KD, Kawasaki Disease; EBV, Epstein Barr Virus; CMV, Citomegalovirus; EGDS, esophagealgastrodudenal serie; PE, plasma exchange.

Guillain-Barré syndrome (GBS) is an acute symmetrical paralyzing disease. The main modalities for the treatment include plasmapheresis and intravenous immune globulin (IVIG). In cases in which IVIG failed, treatment has not been established, however in refractory Kawasaki disease (KD), IVIG retreatment has proved to be successful.

Herein, we present the case of a girl with Guillain-Barré syndrome with fast progression treated on two occasions with Intravenous Immunoglobulin.

CASE REPORT

A 4-year old girl was treated for an upper respiratory tract infection and diarrhea, 1 month and 4 days prior to her admission, respectively.

On August 4th, 2010, when she woke up she noticed generalized weakness, and she had a fall later the same day; she had respiratory and swallowing difficulty with sialorrhea. She was diagnosed by a pediatric neurologist with Guillain-Barré Syndrome, and was given a pulse of methylprednisolone 30 mg/kg/d. Given the fast progression of her condition she was transfered to the Instituto Nacional de Pediatría.

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On August 5th, she arrived with respiratory difficulty, Silverman Anderson of 5, sialorrhea, absence gag reflex; there was flaccid paralysis with predominance in the lower extremities, muscular strength was 2/5 in the upper extremities and 1/5 in the lower ones. There was areflexia, absence of abdominal cutaneous reflexes, hypotonic external and internal anal sphincter, superficial sensitivity was present, as her condition worsened it was decided to intubate her. She was given intravenous human mmmunoglobulin 2 mg/kg in one dose. Cultures for *Campylobacter jejuni* and poliovirus were negative. Cytological albumin dissociation was present in the cerebrospinal fluis, Ziehl-Nielsen and VDRL were negative. Viral serology (VEB, CMV, herpes virus, enterovirus) was negative.

On August 6th, the diagnosis of GBS was confirmed: neurophysiologic studies showed motor polyneuropathy, demyelinating and axonal mixed type (axonal predominance) in upper and lower extremities, without sensorial involvement at that stage. There was no improvement of her neurological condition. Ventilatory support was continued.

On August 9th, she developed ventilator associated pneumonia, *Streptococcus pneumoniae* 100,000 UFC/mL was isolated and she was treated with ceftriaxone. Due to the lack of neurological response and to the development of severe sepsis, it was decided to administer a new dose of IVGG 2 mg/kg/do in a 5 day schedule on August 11th. The course of the neurological state, showed slow improvement. She was extubated on September 2nd, and kept on phase II of ventilation. She also showed 1-2/5 improvement in muscular force, as well as in distal movements (fingers of hands).

On September 8th, she displayed respiratory deterioration, with Silverman Anderson of 5-6; 75% saturation. A bronchoscopy showed total right athelectasis and traqueoendobronchitis which necessitated intubation and treatment with methylprednisolone 1 mg/kg/d and fluticasone. At that stage the patient tone and generalized muscular strength were present in 2/5.

On September 15th she was weaned from ventilatory support and she was able to say some words; five days later an EGDS was normal. Oral feeding was possible. She was discharged one week later. Her international scale of discapacity was grade 4. Carbamazepine 10 mg/kg/d and neuro-rehabilitation schedule were prescribed.

On November 19th, she showed up in the Immunology Service walking with the support of her mother. She could feed herself. She was not taking any medications. Rehabilitation and follow up will continue in our Service.

DISCUSSION

Guillain-Barré syndrome is an acute immune-mediated polyneuropathy. A number of specific endogenous antigens including myelin P-2, ganglioside GQ1b, GM1, and GT1a may be involved in its physiopathology, molecular mimicry of the triggering pathogens resembling antigens on peripheral nerves leads to an excessive autoimmune response mounted by T-cell lymphocytes and macrophages [5].

In adults the first large trial to show a positive effect of immunotherapy was the North American plasma exchange (PE) study, lately the first randomize controlled trial on the use of intravenous immunoglobulin (IVIG) was published in 1992, and showed that IVIG is as effective as PE to reduce the time for functional recovery [6].

Since the publication of these results, IVIG in a regimen of 0.4 g/kg body weight daily for 5 consecutive days or 2 g/kg administered in 1-2 days, has replaced PE as the preferred treatment in many centers, mainly because of its greater convenience and availability. The Cochrane review found no differences between IVIG and PE with respect to the improvement in disability grade after 4 weeks, in the duration of mechanical ventilation, mortality, or residual disability. Presently, IGIV is considered to be the first-line treatment for patients with GBS [7,8].

Korinthenberg et al, in 2005 published a randomized trial aimed to determine the optimal treatment for childhood GBS. They were not able to show that early IVIG treatment diminish subsequent severity, nor a faster recovery in children treated with 2 g/kg body weight IVIG in two days compared with 0.4 g/kg in 5 days. They observed significantly earlier transient relapses (or treatment related fluctuations) among children treated for 2 days, and concluded that the 2 schedules of IVIG were equally well tolerated, with only mild transient side effects [9].

Kawasaki disease (KD) is a well defined condition in which several cases were unresponsive to the initial treatment with IVIG; the risk factors are well known and eventually require "re-treatment" with a second dose of IVIG [10]. On the other hand, approximately 10% of GBS patients deteriorate after initial improvement following the

treatment, the so called "treatment related clinical fluctuations". These are more frequently seen in relatively young patients with severe motor and sensory involvement associated with a preceding and possibly ongoing cytomegalovirus infection, but the best option for these patients is unknown.

Whether these patients need PE after they have been treated with IVIG has not been investigated, but the combination of PE followed by IVIG is not better than PE or IVIG alone. A study in a small series of adult patients investigated the effect of a second course of IVIG in severe unresponsive patients and suggested that it could be effective, but there is not a recent study confirming this suggestion [11].

The case we report herein shows the troublesome clinical fluctuations. Due to the critical condition of the patient we decided to administer a second dose of IVIG which improved the scale of disability and prompted the discharge of the patient.

Retreatment of IVIG and partial responsive GBS could be a therapeutic option especially in severe cases like ours.

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