Case Report

Access this article online

Quick Response Code:

Website:
www.ajts.org

DOI:
10.4103/ajts.ajts_88_21

Effectiveness of therapeutic plasma exchange in case of rare neurological disorder Isaacs syndrome

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Abstract:

Isaacs syndrome is a disease characterized by nerve hyperexcitability and pseudomyotonia and treated with immunomodulatory and symptomatic therapy approaches. Here, we report a case of anti-(leucine-rich glioma-inactivated 1) antibody-positive patient diagnosed as Isaacs syndrome and accomplished a nearly complete response to only four sessions of therapeutic plasma exchange (TPE). Our experience suggests that TPE along with other immunomodulatory agents may be beneficial and well-tolerated approach in patient with Isaacs syndrome.

Keywords:

Antibodies against voltage-gated potassium channel, electromyogram, therapeutic plasma exchange

Introduction and Case Report

Isaacs syndrome is a rare humorally mediated autoimmune neuromuscular disorder, characterized by continuous twitching of muscles at rest, diminished reflexes, progressive muscle stiffness, and neuromyotonia with a prevalence of <1/1,000,000 usually affecting people between 15 and 60 years of age.[1-3] It primarily involves peripheral nerves with blockade of the outward going potassium current and formation of antibodies against voltage-gated potassium channels (Anti-VGKC).[4] This forms the basis of treatment and utilization of plasma exchange for short-term relief and reduction of neuromyotonia.[5-7] We report a case of a 17-year-old male, who presented with a history of pain in both legs, especially calf muscles for 10 months followed by a burning sensation in the dorsum of the foot for 6 months (1–2 times/day for 6 months duration). He was treated at outside local hospital with conservative approach including pain-relieving agents (tablet acelofenac SR 100 mg two times a day/Si opus sit (SOS)), antiepileptics (tablet phenytoin 100 mg two times a day for 2 weeks), and multivitamins (tablet neurobion forte, once a day for 1 month). His condition worsened for the past 2 months, and he had generalized body aches, muscle stiffness, excessive sweating, and continuous twitching of muscles with 5–6 episodes/day of symptoms, over a span of 30 min, mostly in the evening time, and extend to such a degree that he had to take analgesics to relieve symptoms. Symptoms worsened further and progressed to pinprick sensation (paresthesia and dysesthesia) in both the soles of the foot with excessive foul-smelling sweating (5–6 episodes/day). He also complained of insomnia (3 times/week for the past 3 months), continuous twitching of muscle sensation (5–6 times/day for the past 1 month) along with myokymia (2–3 episodes/day), all over the body, and tremors in both hands in resting position.

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Submitted: 05-07-2021
Revised: 04-09-2021
Accepted: 14-01-2022
Published: 12-12-2022

How to cite this article: Tripathi PP, Kumari S, Prabhat N, Lamba DS, Hans R, Goyal MK, *et al.* Effectiveness of therapeutic plasma exchange in case of rare neurological disorder Isaacs syndrome. Asian J Transfus Sci 2023;17:117-20.

Complete hemogram and other routine investigations were within normal limits except anti-leucine-rich glioma-inactivated 1 (LGI1) antibody (positive) and electromyogram (EMG) which revealed a neurogenic hyperexcitability pattern. Other autoimmune panel antibodies such as contactin-associated protein-2 (Caspr2) were negative. Based on clinical history, antibody testing, and the EMG pattern, the diagnosis of Isaacs syndrome was made. As a part of the treatment protocol for this patient, a call for therapeutic plasma exchange (TPE) was received in the Department of Transfusion Medicine. After an initial assessment, plasma exchange for this patient was started on every alternate day from the next day of admission. The estimated total blood volume of the patient was 3900 ml with a weight of 60 kg and the mean plasma volume was 2184 ± 27.57 ml. On average, 2207 ± 28 ml of plasma (1–1.5 plasma volume) was exchanged using an Optia® Spectra automated cell separator (Terumo BCT, Lakewood, Co) using 5% human serum albumin and 0.9% normal saline as replacement fluid (70% and 30%, respectively[8]) with both peripheral vein line catheter access. Injection calcium gluconate (1%) was given throughout all procedures with separate venous line and in addition to replacement fluids. The patient was monitored throughout all procedures for any signs of adverse effects. The patient's details and procedural parameters details are shown in Table 1. Along with plasma exchange, pulse therapy of intravenous methylprednisolone (1 mg/kg/day for 5 days) and antiepileptic drugs (phenytoin 100 mg BID and gabapentin 400 mg BID) were also started. The patient was discharged after 10 days of hospital admission and on regular follow-up.

Effectiveness of therapeutic plasma exchange with follows up

Marked improvement was seen after each plasma exchange. There was immediate remission of pain and muscle twitches after the first plasma exchange session. The degree and frequency of resting myokymia, generalized body ache, and hyperhidrosis were on decreasing trend after each plasma exchange and disappeared after 4th plasma exchange. The patient was on improving trend with decreased in pain sensation and contracting muscle sensation at the end of all plasma exchange sessions as the patient did not require any pain-relieving medications after the first plasma exchange. The patient was discharged after four procedures. At 3 months of follow-up, there was a significant clinical improvement (including the absence of neuromyotonia, generalized body aches, insomnia, and reduction in muscle twitching and stiffness) and at 6-month follow-up, there were no symptoms of any illness and the patient was able to do his normal routine daily work. At present, he is on a tapering dose of phenytoin and gabapentin with normal blood counts and liver function tests.

Discussion and Conclusion

Isaacs' syndrome present with peripheral nerve hyperexcitability phenomenon in which there is a shift of resting membrane potential towards lesser negative values leads to exponential the firing of neurons in the peripheral nervous system.[9] This syndrome is a humoral mediated dendrotoxin-sensitive fast potassium channelopathy. Studies reported approximately 35% of cases with anti-VGKC.[9,10] These antibodies decrease the density of functional VGKCs, which further lead to an increase in the expression of sodium channels and decrease in out flux of the potassium channel, contributing to neuron sensitivity to neuroexcitability and ectopic discharges. Literature mentioned that those other antibodies causing Isaacs syndrome include antibodies directed against LGI1 (as in our case), Caspr2, and other unknown proteins that form a complex with VGKC. These antibodies are against protein complexes

Table 1: Detailed plasma exchange sessions

Parameter	Session 1	Session 2	Session 3	Session 4
PV (ml)	2223	2145	2184	2184
Red cell volume (ml)	1677	1755	1716	1716
Any complication	Severe pain in both legs	Nil	Nil	Nil
PV exchanged (ml)	1708	2297	2246	2577
PV	0.8	1.0	1.0	1.2
Clinical neurological signs and symptoms	Improved after PLEX	Improved after PLEX	Disappeared after PLEX	Disappeared after PLEX
Bilateral lower limb pain	Decreased	Decreased	Decreased	Decreased
Continuous muscle twitching	Decreased	Decreased	Decreased	Decreased
Insomnia	Decreased	Decreased	Absent	Absent
Burning sensation over dorsum of feet	Decreased	Decreased	Disappeared	Disappeared
Hyperhidrosis	Decreased	Decreased	Disappeared	Disappeared
Generalized body ache	Decreased	Disappeared	Disappeared	Disappeared
Myokymia	Improved	Improved	Disappeared	Disappeared
Medications (tablet gabapentin)	Started 400 mg BID	Reduced 200 mg BID	Not requiring	Not requiring

PLEX=Plasma exchange, PV=Plasma volume, BID="bis in die" (Twice a day)

Table 2: Literature review in patients with Isaacs syndrome treated with plasma exchange or immunoadsorption plasmapheresis or plasmapheresis or intravenous immunoglobulin

Studies	Procedure	Number of patients of Isaacs syndrome or neuromyotonia	PV	Duration and frequency	Number or sessions	Replacement fluids	Outcome
Jaben and Winters[15]	PLEX	1	1	Total 8 days on every alternate day	4	5% albumin and 0.9% normal saline	No improvement
Orsucci *et al*.[16]	PLEX	1	1	Total 10 days on every alternate day	5	Not mentioned	Improved
Ishii *et al*.[5]	PLEX/IVIG	1	1	Total 6 days on every alternate day	3	Not mentioned	Improved
Bin Waqar[9]	IAP	1	Not mentioned	6 weeks consecutively	Not mentioned	Not mentioned	Improved
Ibrahim *et al*.[17]	PP	1	1	Total 10 days on every alternate day	5	Not mentioned	Improved
Nakatsuji *et al*.[18]	IAP	1	1	Total 17 days on every 3rd days	6	Not mentioned	Improved
Our case report	PLEX	1	1-1.5	Total 8 days on every alternate day	4	5% albumin and 0.9% normal saline	Improved

PP=Plasmapheresis, IAP=immunoadsorption PP IVIG=Intravenous immunoglobulin, PLEX=Plasma exchange, PV=Plasma volume

to potassium channels instead of the whole channel by itself.[9-11] Continuous contraction or twitching of muscles are pathological features in Isaacs' syndrome related to autoimmune complexes. TPE is an effective line of treatment for these patients as TPE results in the removal of pathogenic material as reported in the literature.[5,12] Treatment options due to fewer incidence of VGKC-complex antibody-associated diseases are limited.[11] Steroids are basic drugs along with any combination therapy. According to the American Society for Apheresis 2019, TPE for VGKC antibodies comes under category II 1(B).[13] Reported cases in literature with VGKC antibodies are very few to date (<100 cases). Vincent *et al*. (2004) reported complete resolution of symptoms in 4 out of 7 patients in VGKC antibodies positive patients where TPE was administered in conjunction with steroids and intravenous immunoglobulin. Almost similar results were shown by Jaben and Winters with the effective use of plasma exchanges.[15] Another study by Skeie *et al*. mentioned that effective clinical improvement lasting about 6 weeks with a fall in VGKC antibody titers and reduction in electromyography can be often produced by TPEs.[7,14] Studies mentioning the effectiveness of TPE are mentioned in Table 2.[5,9,15-18] In addition, pulse therapy and antiepileptic drugs might have adjuvant effects with TPE. Clearance rate of these drugs is very less with plasma exchanges due to less protein binding and extravascular distribution.[19] To the best of our knowledge, this is the first case reported in the literature from North India with significant clinical benefit from TPE. More cases have to be reported for establishing the therapeutic role TPE in neurological conditions like Isaacs syndrome along with other immunomodulation therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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