Immunoglobulin-Induced Aseptic Meningitis in Juvenile Dermatomyositis: A Case Report

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Case Report

Keywords: Intravenous immunoglobulin, aseptic meningitis, juvenile dermatomyositis

Posted Date: November 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1109819/v1

Abstract

Background: Aseptic meningitis is a known but unusual serious adverse effect of intravenous immunoglobulin (IVIG). It usually resembles infectious meningitis which makes diagnosis challenging.

Case presentation: We report a five-and-a-half-year-old Chinese girl with juvenile dermatomyositis presented with signs of meningismus 21 hours after the initiation of IVIG infusion. Her blood work at diagnosis showed neutrophilia and lymphopenia. The cerebrospinal fluid analysis demonstrated neutrophilic pleocytosis, hyperproteinorrachia and normoglycorrhachia. All microbiological tests were negative. The child recovered fully within 72hours without neurological sequelae.

Conclusion: IVIG-induced aseptic meningitis remains a diagnosis of exclusion. Although it is rare, paediatricians should be aware of this complication and avoid unnecessary investigation or treatment.

Background

Aseptic meningitis is a known severe adverse effect of immunoglobulin. It usually resembles infectious meningitis, which makes diagnosis challenging. Its causes are either infective or non-infective (also called aseptic), consisting of autoimmune, neoplasia and iatrogenic etiologies.[1]

Intravenous immunoglobulin (IVIG) is widely used for a broad range of diseases, including immunodeficiencies, neuromuscular diseases and autoimmune diseases. The treatment of juvenile dermatomyositis (JDM) with IVIG is generally accepted to be effective as a second-line option, particularly for steroid-resistant patients or those with predominant skin activity.[2–4] A retrospective JDM cohort in 2011 demonstrated IVIG efficacy in controlling disease activity.[5]

We herein report a five-and-a-half-year-old girl with JDM, who had no adverse events with IVIG (Intragam P^{TM}) administration, but subsequently developed IVIG-induced aseptic meningitis after switching to another formulary IVIG (Privigen^{TM}). The possible risk factors for developing aseptic meningitis are discussed.

Case Presentation

Our patient was a Chinese girl who initially presented with proximal muscle weakness and limping gait at four years old. She also demonstrated dermatological features including heliotrope rash over facial region, and Gottron's papules over her metacarpophalangeal and interphalangeal joints with cutaneous ulcerations. She had raised serum creatine kinase up to 1400IU/ml, and her MRI showed features of myositis over her bilateral shoulders, arms and thigh muscles. She was given the diagnosis of juvenile dermatomyositis. Her childhood myositis assessment score (CMAS) was five out of 52 points.

She was initially treated with intravenous methylprednisolone, subcutaneous methotrexate and six doses of monthly IVIG (Intragam P^{TM}) at presentation. The IVIG was administered with the dosage of 1gram/kg (total 15 grams in volume of 250 ml) over nine hours each day for two consecutive days. She had no adverse reaction towards the medication. She responded well to treatment and her muscle power improved with CMAS 43 out of 52 four months later. Her steroid was gradually tapered down, but she developed worsening vasculitis with necrotic lesions as well as chondritis over both ears. Her skin condition remained refractory despite increasing the steroid and methotrexate dosage, as well as adding oral cyclosporin A. Cyclosporin A was subsequently switched to oral cyclophosphamide and another course of IVIG was given in order to optimize the control of her skin activity at the age of five and a half. Due to a change in our hospital drug formulary, our patient received Privigen^{TM} instead. She was given 2grams/kg (total 32.5 grams with volume of 325 ml), which was infused over 11 hours.

She was asymptomatic during the infusion, but developed high fever, headache and repeated vomiting 10 hours after the end of the infusion. Her temperature was up to 40 degree Celsius. She also complained of neck pain and photophobia. There was no history of seizure, altered state of consciousness or abnormal behavior. Physical examination demonstrated meningismus with neck stiffness and positive Kernig's sign. There was no other focal neurological sign.

Her blood tests showed raised white cell count to 24 x10^9/L with neutrophilia (absolute neutrophil count 17.3 x10^9/L), but normal C-reactive protein (0.7mg/L) and serum procalcitonin level (0.14 ng/ml). The CT brain was normal. The cerebrospinal fluid (CSF) was clear and colorless. Its analysis demonstrated neutrophilic pleocytosis with 2188cells/mm^3 (87% neutrophils) without any eosinophils, hyperproteinorrachia 0.66g/L and normoglycorrhachia (2.9mmol/L in CSF and 4.7mmol/L in plasma). She was initially treated for meningitis with intravenous meningitic dose of meropenem and acyclovir. The cultures from her blood sample and CSF did not isolate any causative organisms.

A lumbar puncture was repeated on day 6 and CSF analysis revealed white cell count of 11cells/mm^3 with 9% polymorphs, normal protein (0.19g/L) and normal glucose (3.6mmol/L in CSF and 5.3mmol/L in plasma). The patient completed a 14-day course of meropenem. With the temporal relation between IVIG administration and the symptoms onset, sterile cultures, as well as normal CRP and procalcitonin, a diagnosis of aseptic meningitis was made.

Her symptoms and fever subsided on day 2 of admission, and she recovered completely without any neurological sequalae.

Discussion

IVIG-induced aseptic meningitis is a rare complication, with an estimated incidence of 0.6-1%.[6,16] It was previously reported during the treatment for immune-mediated neurological disorders and neuromuscular diseases, which were mainly focused in the adult population. Reports on the pediatric population were

relatively scarce. The exact pathophysiology of IVIG-induced aseptic meningitis remains unclear, with postulated mechanisms including direct toxic effect and immunological hypersensitive reaction.

Our patient did have the typical features of IVIG-associated aseptic meningitis described in the literature.[6–7] First, there was a temporal relationship between the onset of the symptoms of aseptic meningitis and the high dose IVIG therapy. Secondly, the symptoms and signs of meningismus quickly resolved within 48 hours in our patient. Thirdly, although the initial blood-work revealed leukocytosis, neutrophilia, and the CSF analysis showed neutrophilic pleocytosis but all cultures were negative. These all fit into the picture of aseptic meningitis induced by IVIG described by Bharath and Kemmotsu.

Evidences concerning both patient and IVIG-related risk factors remain controversial. It had been suggested that history of migraines, female sex and underlying connective tissue disease such as systemic lupus erythromatosus could be potential risk factors for developing aseptic meningitis after IVIG.[13,14,15] Further evidences are needed to evaluate whether juvenile dermatomyositis could be a risk factor.

It is important to note that this was not the first time our patient had IVIG. She developed aseptic meningitis after having IVIG therapy given at a higher dose (2gram/kg) and faster rate (over 11hours). Besides, our patient received a different brand of IVIG Privigen™ from her previous IVIG infusions Intragam P™ prior to her incidence of aseptic meningitis. In regard to IVIG-related risk factors, particularly the dosage and the infusion rate, evidence remains disputable.[8,13] We do not know why some IVIG brands seem to be more likely to cause aseptic meningitis. It was thought that it could possibly be related to the IgA concentration given that the administration of IVIG containing IgA may cause dramatic clinical reactions in patients with serum anti-IgA.[1,21] The IgA content in Privigen™ was 0.025mg/ml which is slightly higher than that of Intragam P™, <0.025mg/ml (Table 1). Although in Bharath's retrospective study, 50% patients developed aseptic meningitis after Privigen™ infusion, due to the small number of patients, the brands of IVIG or varying commercial preparations has not been identified as a risk factor.

Table 1
Compositions of Privigen™ and Intragam P™.

	Privigen™	Intragam P™
IgG 1	67.8%	61%
IgG2	28.7%	36%
IgG3	2.3%	3%
IgG 4	1.2%	1%
IgA	0.025mg/ml	<0.025mg/ml
Excipients	L-proline, WFI	Maltose 10mg/ml

Supportive measures such as analgesics and anti-emetics seem to be sufficient. Corticosteroids do not seem to be effective in treating IVIG-induced aseptic meningitis.[7,12,13] Re-infusions are not contraindicated.[6,16] In case our patient requires IVIG in the future, Privigen™ will be avoided. Switching to subcutaneous preparation could potentially be an effective strategy in attenuating adverse effects.[19] Subcutaneous immunoglobulin (SCIG) was associated with lower rates of aseptic meningitis.[20] There are increasing number of studies show that subcutaneous immunoglobulin (SCIG) can be used in treating various diseases including immunodeficiency diseases, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy etc. Further research is needed to determine its efficiency as an immunomodulatory therapy. Preventive measures including infusing at a slow rate, pre-hydration and adequate fluid intake throughout infusion, as well as premedication with acetaminophen and anti-histamine could be considered.[12]

Milder cases of aseptic meningitis might not necessarily be recognized, given that aseptic meningitis is such a rare complication of IVIG. On the other hand, post-IVIG headache is common. The true Incidence of IVIG-induced aseptic meningitis could be under-reported. Although there is increasing evidence on the self-limitedness of IVIG-induced aseptic meningitis and its temporal profile, the necessity for lumbar puncture and antibiotics remains controversial.[6,17,18] Given that our patient had been treated with several immunomodulatory medications and her increased risks of opportunistic infections, she was treated with intravenous antibiotics.

Conclusion

In conclusion, IVIG-induced aseptic meningitis remains a diagnosis of exclusion. Although it is rare, paediatricians should be aware of this complication and avoid unnecessary investigation or treatment.

Abbreviations

CRP
C-reactive protein
CSF
Cerebrospinal fluid
CT
Computer tomography
IVIG
Intravenous immunoglobulin
JDM
Juvenile dermatomyositis. SCIG:subcutaneous immunoglobulin.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Informed consent was obtained from the parent of the patient for publication of this case report.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

OMC drafted the manuscript and reviewed the literature. CIK, HMRY and WKYC revised the manuscript. All authors contributed to obtaining and interpreting the clinical information. All authors read and approved the final version of the manuscript.

Not applicable

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