

ACUTE ASEPTIC MENINGITIS ASSOCIATED WITH ADMINISTRATION OF IMMUNOGLOBULIN IN CHILDREN: A CASE REPORT AND REVIEW OF THE LITERATURE

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In recent years, intravenous immunoglobulin (IVIG) has been employed in the treatment of an expanding variety of medical conditions, such as immune thrombocytopenic purpura (ITP), Kawasaki disease, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, autoimmune hemolytic anemia, autoimmune neutropenia, acquired hemophilia A, and myasthenia gravis.¹

The effectiveness of IVIG is well documented, and serious adverse reactions to it are unusual. The most frequently encountered adverse effects of IVIG include headache, nausea and vomiting. These symptoms are usually mild and self-limiting, and occur in less than 5% of patients receiving IVIG.² IVIG therapy, however, can in rare cases lead to serious complications, such as hemolytic anemia, thromboembolism, hepatitis, and renal failure.² Additionally, IVIG therapy can be complicated by aseptic meningitis. Until October 1997, only 36 cases of IVIG-associated aseptic meningitis had been described in the literature,³ 12 of whom were children.⁴⁻¹³ Most of these cases had ITP as the primary disease. We recently treated a child with autoimmune neutropenia, who developed aseptic meningitis 24 hours after IVIG therapy. We report our case and review the clinical and laboratory findings and outcome of this rare complication of IVIG therapy in children.

Case Report

The patient was a one-year-old boy with autoimmune neutropenia. The diagnosis was based on a history of recurrent infections and neutropenia since the age of six months. The absolute neutrophil count (ANC) ranged from 0-500/mm³. Bone marrow study revealed active trilineage hematopoiesis with normal differentiating granulopoiesis.

Because neutropenia had been associated with recurrent

infections, therapy with IVIG 500 mg/kg/day for two days was initiated in March 1997. Eight hours after the second IVIG infusion, the child presented with vomiting, irritability, poor feeding, lethargy, and fever. Physical examination revealed a temperature of 39.2°C, pulse 120/min. and respiratory rate of 22/min. The child appeared sick and irritable, and had neck rigidity. Meningitis was suspected. His laboratory data showed a total WBC count of 6.8x10⁹/L with 12% neutrophils, 2% band forms, 66% lymphocytes and 20% monocytes. His platelet count was 451x10⁹/L and hemoglobin was 110 g/L. The total cerebrospinal fluid (CSF) WBC was 1580/mm³ with 49% neutrophils, 22% band forms, 19% lymphocytes, and 10% monocytes. CSF protein was 869 mg/dL and glucose of 4.3 mmol/L, with simultaneous serum glucose concentration of 8 mmol/L. CSF for latex agglutination tests for *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* antigens were negative. CSF gram-stain showed no organisms, and cultures for bacteria, viruses and fungi were negative. Blood culture was sterile.

Initial empiric therapy included intravenous ceftriaxone, which was discontinued after three days when the diagnosis of bacterial meningitis was excluded. The patient became afebrile and playful, and the signs of meningeal irritation disappeared within 48 hours of admission. A repeat complete blood count at this time showed response to IVIG, with the absolute neutrophil count increased to 10157/mm³. The patient was discharged from the hospital three days after admission, and followed up in the outpatient clinic. He had a complete recovery without sequelae.

Discussion

The use of different immunoglobulin preparations has recently been extensive. During the last 10 years, an estimated total of 10 tons of IVIG were produced annually. Intravenous immunoglobulin has been used in a variety of diseases, including primary immunodeficiencies, pediatric acquired immunodeficiency syndrome (AIDS), infections in low birth weight infants, bone marrow transplantation, chronic lymphocytic leukemia (CLL), idiopathic

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TABLE 1. *Clinical and laboratory findings of acute aseptic meningitis associated with IVIG therapy in 13 children.*

Underlying diagnosis	Age (yr)/sex	IVIG dose g/kg/day	# of doses	Onset of symptoms	Protein mg/dL	Glucose mg/dL	CSF WBC x 10 ⁹ /L	% PMNL
ITP	2/F ¹⁶	0.4	Not mentioned	7 days	21	Normal	540	69
ITP	2/F ⁹	0.4	3	48 hr	86	40	3026	47
ITP	Child ⁶	Not mentioned	Not mentioned	36 hr	Not mentioned	Not mentioned	Not mentioned	Not mentioned
ITP	7/M ⁷	0.4	2	1 hr after second dose	450	19.8	245	88
ITP	7/M ⁵	0.4	2	12 hr after second dose	566	62	1620	95
ITP	8/M ⁵	0.4	3	Not mentioned	420	60	6670	95
ITP	9/M ⁸	0.4	2	12 hr after second dose	600	73.8	2500	98
ITP	10/M ⁴	1.0	2	6 hr after second dose	310	70.2	2860	3
ITP	14/F ²³	0.6	2	Second day	1380	Normal	1830	83
CIDP	Child ⁹	0.4	5	Fifth day	320	Not mentioned	200	90
AIN	2/F ³	1	2	24 hr	88	6	3500	95
KD	5/M ¹¹	Not mentioned	Not mentioned	1 hr	Not mentioned	Not mentioned	Not mentioned	Not mentioned
AIN	1/M (present case)	0.5	2	8 hr	869	77.4	1580	47

ITP=idiopathic thrombocytopenic purpura; CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; AIN=autoimmune neutropenia; KD=Kawasaki disease.

thrombocytopenic purpura (ITP), Kawasaki syndrome, autoimmune neutropenia and demyelinating polyneuropathies.¹⁻⁶ They are generally used for: 1) replacement therapy of primary and secondary immunodeficiencies; 2) specific passive immunotherapy; 3) prophylaxis and treatment of infectious diseases; and 4) management of specific inflammatory and/or immunologic disorders.^{1-5,13}

Aseptic meningitis has been reported in association with the administration of many drugs, including anti-inflammatory drugs (ibuprofen, naproxen), antimicrobial agents (sulfonamides), chemotherapeutic agents (cytosine arabinoside and methotrexate), chemicals/irritants (detergents), and intravenous immunoglobulin.⁴ The exact mechanism by which a drug or a chemical induces aseptic meningitis is not well known, but possible mechanisms include hypersensitivity reaction, stabilizing products, cytokines, cerebrovascular sensitivity and direct meningeal irritation.⁴

IVIG-related meningitis presents a unique clinical dilemma, because many of the patients treated with IVIG have underlying diseases which predispose them to central nervous system complications, such as meningitis (in those with immunodeficiency) and intracranial bleeding (in those with ITP). Therefore, once meningitis is suspected, these patients receive prompt evaluation, including CSF studies. Such early evaluation explains the CSF findings which mimic those of bacterial or early viral meningitis.¹⁰⁻¹⁸ The resulting inability to readily distinguish this syndrome from bacterial infection often necessitates empiric antibiotic therapy. Additionally, many such patients with ITP require CT scan of the brain to rule out intracranial bleeding before obtaining CSF for analysis.

Of the 36 cases of IVIG-associated aseptic meningitis reported in the English language literature, 12 were children, 9 of whom had ITP. Of the three other patients, one had autoimmune neutropenia, one had Kawasaki disease, and the other had chronic inflammatory demyelinating polyradiculoneuropathy.^{3-9,14,16,20,23} Relevant clinical and laboratory findings of these cases are shown in Table 1. In most cases, signs and symptoms occurred within 48 hours of IVIG infusion, however, some cases presented as late as seven days after the therapy (range 1 hour to 7 days). Symptoms and signs were not different from those associated with bacterial or viral meningitis, and included headache, fever, vomiting, nuchal rigidity and photophobia. Furthermore, the CSF findings were similar to those reported in patients with early acute aseptic meningitis. The CSF WBC count ranged from 200-6670x10⁹/L, with predominance of polymorphonuclear cells. In most cases, CSF protein concentrations were mildly to moderately elevated, with normal CSF glucose concentration. There were no long-term sequelae reported.

Resolution of the clinical manifestations occurred within hours to days, after discontinuation of IVIG therapy. No deaths or long-term sequelae have been reported so far. Occasionally, recurrent IVIG-associated meningitis has been reported after repeated IVIG infusions. Whether the rare patient with recurrent aseptic meningitis should have repeated CSF studies with each episode is not known at this stage.¹⁹

References

1. Mobini N, Sarela A, Ahmed AR. Intravenous immunoglobulin in the therapy of autoimmune and systemic inflammatory disorders. *Ann*

- Allergy Asthma Immunol 1995;74:119-28.
2. Duhem C, Dicato MA, Reis F. Side effects of intravenous immunoglobulins. *Clin Exp Immunol* 1994;97(Suppl 1):79-83.
3. Short AF, Kester KE. Meningitis and hepatitis complicating intravenous immunoglobulin therapy. *Ann Pharmacol* 1996;30:1115-6.
4. Preminger-Shapiro R, Nussinovitch M. Aseptic meningitis: a frequent side effect of intravenous immunoglobulin. *Eur J Pediatr* 1995;154:866-7.
5. Pallares DE, Marshall GS. Acute aseptic meningitis associated with administration of intravenous immunoglobulin. *Am J Pediatr Hematol Oncol* 1992;14:279.
6. Kressebuch H, Schaad UB, Hirt A, Bianchetti MG. Cerebrospinal fluid inflammation induced by intravenous immunoglobulin. *Pediatr Infect Dis J* 1992;11:894-5.
7. Ozsoylu S. Aseptic meningitis and intravenous gammaglobulin treatment. *Am J Dis Child* 1993;147:129-30.
8. Van Daele MC, Wijndaele L, Hunnink K. Intravenous immunoglobulin and acute aseptic meningitis. *N Engl J Med* 1990;323:614-5.
9. Rao SP, Teitelbaum G, Miller ST. Intravenous immune globulin and aseptic meningitis. *Am J Dis Child* 1992;146:539-40.
10. De Vlieghere FC, Peetermans WE, Vermeylen J. Aseptic granulocytic meningitis following treatment with intravenous immunoglobulin. *Clin Infect Dis* 1994;18:1008-10.
11. Kato E, Shindo S, Eto Y, Hashimoto N, et al. Administration of immunoglobulin associated with aseptic meningitis. *JAMA* 1988;259:3269-71.
12. Nydegger UE. Safety and side effects of IV immunoglobulin therapy. *Clin Exp Rheumatol* 1996;(Suppl)14:S53-S56.
13. Vera-Ramirez M, Charlet M, Parry GH. Recurrent aseptic meningitis complicating intravenous immunoglobulin therapy for chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 1992;42:1636-7.
14. Marinac JS. Drug and chemical-induced aseptic meningitis: a review of the literature. *Ann Pharmacol* 1992;26:813-20.
15. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Int Med* 1994;121:259-62.
16. Harati Y, Shaibani AT. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Int Med* 1995;122:316-7.
17. Webster ADB. Intravenous immunoglobulins of benefit in primary hypogammaglobulinaemia. *BMJ* 1991;303:375-6.
18. Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Int Med* 1994;121:305-6.
19. Molina J, Coffineau A, Rain J, Letonturier D, Modai J. Aseptic meningitis following administration of intravenous immunoglobulin. *Clin Infect Dis* 1992;15:564-5.
20. Talan DA, Zibulewsky J. Relationship of clinical presentation to time to antibiotics for the emergency department management of suspected bacterial meningitis. *Ann Emerg Med* 1993;22:1733-7.
21. NIH Consensus Conference. Intravenous immunoglobulin prevention: treatment of disease. *JAMA* 1990;264:3189-93.
22. Fischer GW. Therapeutic uses of intravenous gammaglobulin for pediatric infections. *Pediatr Clin North Am* 1988;35:517-24.
23. Watson JDG, Gibson J, Joshua DE, Kronenberg H. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy. *J Neurol Neurosurg Psychiatr* 1991;54:275-6.