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IVIG as a Cause of Fatal Acute Ischemic Stroke: Case Report and Systematic Review

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Abstract

Purpose— To highlight the role of intravenous immunoglobulin (IVIG) in patients with malignant acute ischemic stroke.

Case Description—A 39-year-old woman developed posterior cerebral artery infarctions bilaterally without any large arterial occlusion identified on CT angiography after being treated with IVIG for acute inflammatory demyelinating polyneuropathy. The patient's neurological deficits progressed to brain death over the next 36 hours.

Literature Review— A comprehensive and systematic review of the literature concerning IVIG administration associated with ischemic and/or embolic events was conducted, and a total of 24 articles were included for review. Thirteen (54.2%) studies described post-IVIG stroke, 6 (25.0%) cerebral infarction, 6 (25.0%) deep vein thrombosis, 5 (20.8%) myocardial infarction, 3 (12.5%) pulmonary embolism, 2 (8.3%) multiple embolic events, and 4 (16.7%) other embolic events. Review of the 24 included articles revealed that IVIG may be associated with a risk of embolic and ischemic complications.

Summary— This case report and literature review highlight the need for studying the mechanism of association and identifying new strategies to reduce ischemic stroke during or after IVIG administration.

Keywords— Ischemic stroke, intravenous immunoglobulin, acute cerebral artery thrombosis.

INTRODUCTION

Pooled intravenous immunoglobulin (IVIG) is used to treat various neurological diseases due to anti-inflammatory and immunomodulating effects.[29] Consisting primarily of IgG, with some IgA and IgM contents, the potential mechanisms of action of IVIG include inactivation of T cells that promotes an anti-inflammatory Th2 cytokine milieu and decreases antibody production by B cells.[14] Although the standard IVIG dose of 0.2–0.4g/kg bodyweight administered 3 times weekly was initially established as the recommended maintenance dose for patients with antibody deficiency syndromes,[17] IVIG dosing varies depending on the underlying pathologic condition. For example, for patients presenting with Guillain–Barré Syndrome, the standard recommended daily dose is 0.4 g/kg for 5 consecutive days,[38] whereas the daily dose for chronic inflammatory demyelinating polyneuropathy ranges from 1.0–2.0g/kg, depending on whether a loading or maintenance dose is being given.

At the standard dose of 0.2–0.4 g/kg given 3 times weekly, common adverse effects are headache, aseptic meningitis, and mild transfusion reactions.[27] Major adverse events include[15] anaphylaxis, autoimmune hemolytic anemia, neutropenia,

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and acute renal failure.[1,4,9,39] Additionally, although rare, thromboembolism,[27] including myocardial infarctions, acute coronary syndromes, and cerebral ischemia, can occur in approximately 0.08% of patients.[9,36,39] Specifically, cerebral sinus thrombosis is a known complication of IVIG therapy,[23] and cerebral sinus thrombosis has been associated with venous infarctions.[26] Here, we present a case of fatal ischemic stroke in a 39-year-old woman following treatment with IVIG for acute inflammatory demyelinating polyneuropathy. In addition, we provide a systematic review of the literature pertinent to IVIG administration associated with ischemic and/or embolic events.

CASE DESCRIPTION

Initial Presentation, Physical Examination, and Management

A 39-year-old woman presented to an outside hospital with complaints of rhinorrhea, sore throat, cough, headache, and diarrhea for 2 days, accompanied by fever, left-sided weakness, and fatigue. She sustained a fall with no significant traumatic injuries or loss of consciousness. Her medical history was remarkable for a seizure disorder (on levetiracetam), hypothyroidism (on levothyroxine), autism, obsessive-compulsive disorder, and hyperlipidemia. The patient was never a cigarette smoker and did not drink alcohol. Her family medical history could not be obtained. At baseline, she resided at a high-functioning group home with no recent history of illnesses or symptoms although members of the home were recently ill (details unknown) during the 2 weeks prior to her presentation.

Physical examination was largely unremarkable, except for excessive spitting by the patient throughout the examination and signs of throat inflammation concerning for uvulitis. Otherwise, cardiac, pulmonary, abdominal, neurological, and joint and extremity examinations were unremarkable.

Initial workup consisting of an influenza test, urinalysis, electrocardiogram, and chest x-ray, all of which were normal. Noncontrast computed tomography (CT) of the head and spine was normal, except for signs of uvulitis. She was admitted to the outside hospital, and azithromycin was initiated for a presumed upper respiratory infection.

Acute Change in Physical Examination and Transfer to Tertiary Center

Overnight, the patient had increasing oral secretions and became unable to swallow her medications, requiring insertion of a nasogastric tube. Shortly thereafter, her fatigue and generalized weakness acutely worsened, and she became quadriparetic. Her speech was unintelligible, and she had bilateral ptosis and no gag reflex. She was immediately intubated and transferred to the intensive care unit. Further workup revealed leukocytosis and bilateral infiltrates on her chest x-ray. She was subsequently transferred to our tertiary care institution.

The patient arrived at the tertiary care center, intubated and sedated with intravenous propofol infusion. She had normal general, cardiac, pulmonary (intubated), abdominal, joint, skin, and head and neck examinations. On neurological examination, the patient was awake, alert, and able to signal or reply by hand who and where she was. She was unable to speak but was able to grossly comprehend and follow basic commands, such as sticking out her tongue and blinking twice consistently. Pupils were equal, round, and reactive to light with a positive red reflex. Visual fields were full, and she was able to track light. Extraocular movements were intact with no nystagmus. She was able to close her eyes tightly but had difficulty opening them. Face was symmetric. Auditory acuity was grossly intact. Tongue was midline. With respect to motor strength, the patient had normal muscle bulk but was diffusely hypotonic. She had minimal to no movement in all 4 extremities (0 to 1 out of 5 strength in all 4 extremities) to command or noxious stimuli. No reflexes were elicited in all 4 extremities. No Babinski or Hoffman signs were elicited. No improvement or change was observed in the patient's examination findings from hospital day 1 (presentation to tertiary care center) to hospital day 8.

Workup and Imaging

A lumbar puncture demonstrated an opening cerebrospinal fluid pressure of 27cm H2O, and a closing pressure of 13cm H2O. Cerebrospinal fluid analysis revealed albuminocytologic dissociation, with 1% neutrophils and protein mildly elevated at 66mg/dL. On electromyography and nerve conduction studies, no compound muscle or sensory nerve action potentials were elicited, despite maximal stimulation. Furthermore, no denervation potentials were present, and fast repetitive stimulation also showed no response.

Laboratory tests, including anti-acetylcholine receptor antibodies, anti-NMDA receptor antibodies, acid-fast and fungal blood culture, aerobic and anaerobic blood cultures, thyroid-stimulating hormone, vitamin B12, Lyme disease screening, fluorescent treponemal antibody screen, and a cerebrospinal fluid viral panel (cytomegalovirus, enterovirus, herpes simplex virus 1 & 2, and Epstein-Barr virus), were all unremarkable or negative. Other laboratory tests, including thyroid hormone, thyroid stimulating hormone, troponin level, hemoglobin A1C, prothrombin time, activated partial thromboplastin time, international normalized ratio, and basic metabolic panel were all within normal limits. The only remarkable result was an elevated white blood cell count. Magnetic resonance imaging studies of the brain and cervical spine with and without intravenous contrast material were unremarkable.

Assessment, Plan, Acute Change, and Outcome

Initially, several diagnoses were suspected based on the patient's presentation and examination findings, including acute inflammatory demyelinating polyneuropathy (i.e., Guillain–Barré Syndrome), West Nile virus infection, and botulism. On the basis of the lumbar puncture and electromyography results, the patient was deemed to most likely have an acute polyneuropathy, likely Guillain–Barré Syndrome.

On hospital day 2, the patient was started on a 5-day course of

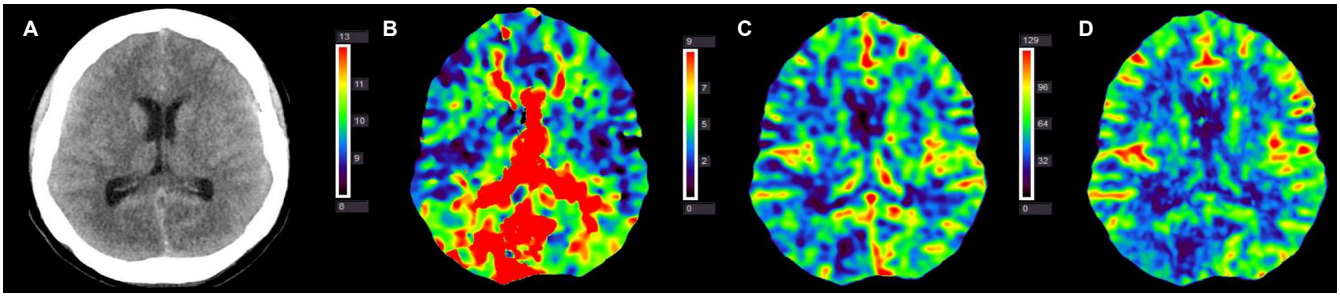

FIGURE 1: Noncontrast computed tomography (CT) scan of the head and CT perfusion images obtained shortly after a change in the patient's neurological examination (no pupillary reflexes) on hospital day 8. Noncontrast CT image reveals hypodensities in the bilateral posterior cerebral artery (PCA) territories and effacement of the gray-white matter junction (A). CT perfusion images show an increased time-to-peak in the right PCA territory greater than the left (B), decreased blood volume in the right PCA territory (C), and corresponding decreased blood flow in the right greater than left PCA territories (D).

IVIG at a dose of 0.2 g/kg and completed her course on day 6. Two days later (hospital day 4), she had an acute neurological change. Overnight, the patient was found have no pupillary or corneal reflexes.

An emergent noncontrast head CT scan and CT angiogram with perfusion imaging were obtained. The CT scan revealed bilateral posterior cerebral artery (PCA) territory hypodensities (right greater than left) without associated hemorrhages, concerning for acute/subacute ischemic stroke (Figure 1A). The CT perfusion angiography images revealed an increased time-to-peak in the right PCA territory with decreased blood volume and flow in that area (Figure 1 B–D).

No large arterial vessel occlusions were visualized on 3-dimensional arterial and venous phase CT angiography reconstructions (Figure 2 A–D). Narrow basal cisterns were identified on the emergently obtained noncontrast head CT scan, which was concerning for cerebral edema. Hydrocephalus also identified on CT scan (Figure 3). The center's neurosurgery team was consulted, resulting in emergent placement of an external ventricular drain for management of hydrocephalus and suspected increased intracranial pressure.

Progression to a malignant stroke was evident based on the compression of the fourth ventricle, lack of cortical sulci, and effacement of the basal cisterns seen on another noncontrast head CT scan obtained 8 hours after the initial change in the patient's neurological examination and findings on the acute neurological examination (Figure 3). Despite supportive care, the patient neurological deficits progressed to brain death over the next 36 hours due to malignant cerebral edema and brain herniation. An autopsy was not performed.

Written consent for the aforementioned treatments and procedures was provided by the patient's family. Institutional review board approval was deemed unnecessary due to the observational nature of the report.

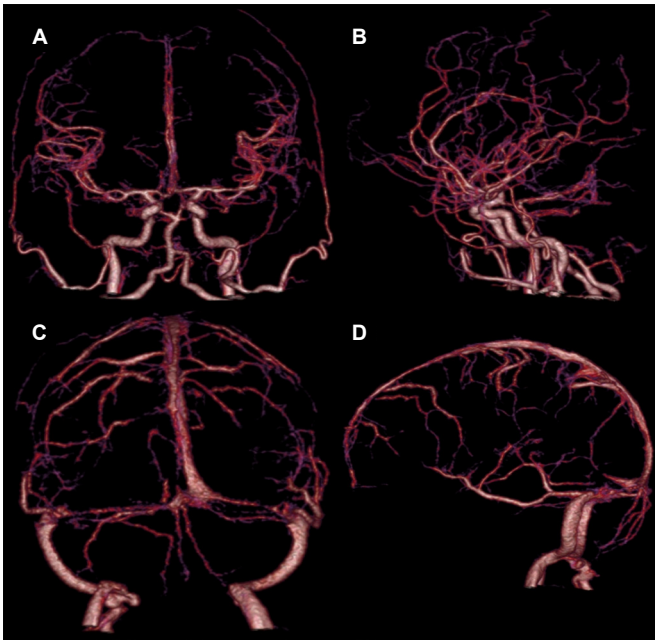

FIGURE 2: 3D reconstructions of arterial and venous phases of CT vessel imaging demonstrate no large vessel occlusions or major or focal occlusion of the venous sinuses and vessels. A and B, respectively, demonstrate anteroposterior and lateral arterial phases of the intracranial vessels. C and D, respectively, demonstrate anteroposterior and lateral venous phases of intracranial vessels.

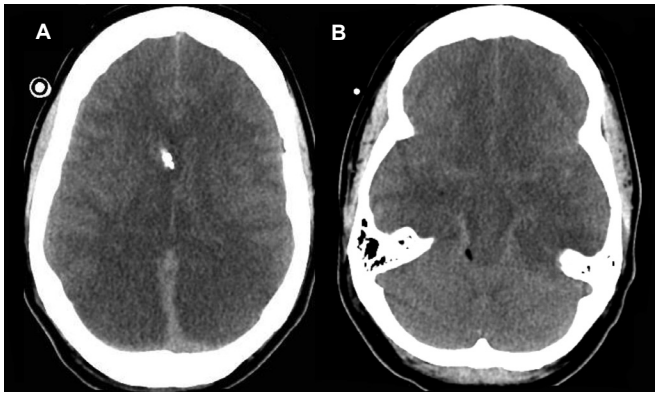

FIGURE 3: Serial noncontrast CT images of the head (A, B) reveal diffuse regions of hypodensity in the bilateral PCA territories with significant edema and effacement of the basal cisterns, indicating malignant bilateral posterior circulation ischemic stroke.

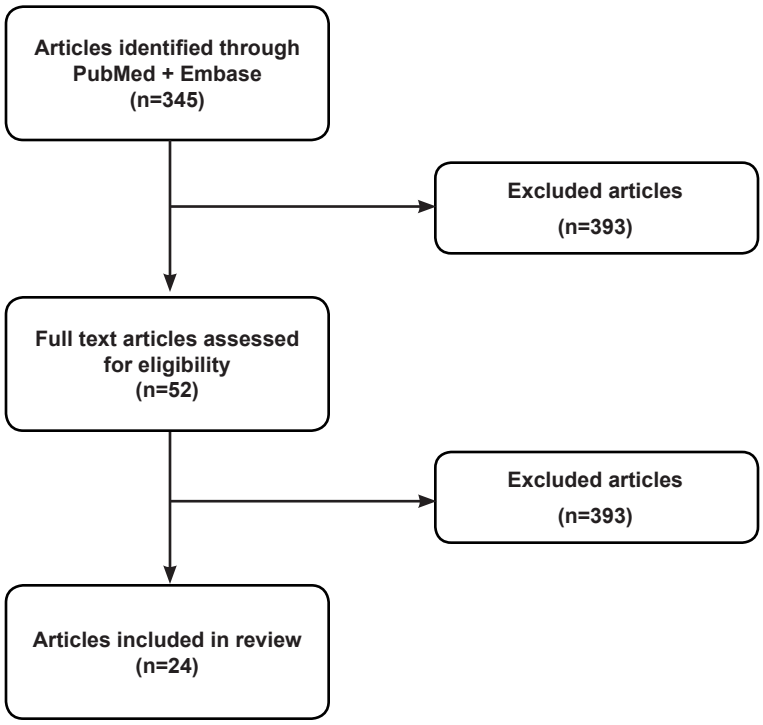

FIGURE 4: PRISMA flowchart for article selection. A total of 24 articles were included.[1,6,7,10-12,16,18-22,25,28,30-32,34,35,37,40,41,43,44] Of the 24 included studies, 16 (66.7%) were case reports, 4 (16.7%) were case series, 1 (4.2%) was a retrospective cohort, 1 (4.2%) was a case-control, 1 (4.2%) was a case-crossover, and 1 (4.2%) was an uncontrolled before-and-after. The majority of the studies (13, 54.2%) originated from the United States. The quality of most included studies was very low or low. The risk of bias of the majority of included studies was high, predisposing this systematic review to a high risk of bias overall. Details of the included studies are found in Table 1.

LITERATURE REVIEW / SYSTEMATIC REVIEW

Methods

A comprehensive and systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using PubMed Medline (National Library of Medicine) and Embase (Elsevier) in combination with a review of eligible article bibliographies.[24] The following MEDLINE search terms including MeSH terms were utilized for the search: [stroke] and [intravenous immunoglobulin]. The literature search was completed on September 18, 2020 with no restrictions on language, date, or article type. No protocol was registered, and no funding was received.

Articles were screened by title and abstract for relevance, and duplicates were removed. The articles progressing past the initial stage of screening were screened for final inclusion based on prespecified inclusion and exclusion criteria. The inclusion criteria were published or translated into an English version, with full text available, discussing IVIG and organ ischemia, DVT, or embolic complications, and presenting primary data. Conference abstracts, preclinical studies, literature or systematic reviews, meta-analyses, and commentaries or letters to the editor were excluded. A second reviewer replicated the search strategy, and disagreements were resolved.

After articles were chosen for final inclusion, a review of pertinent study characteristics was conducted. Study design, country of origin, number of patients receiving IVIG, and number of patients with various ischemic or embolic complications were abstracted. An article that described one or two patients was considered a case report. Quality grades were assigned to included studies in accordance with the GRADE framework, which classifies evidence into one of four levels – high, moderate, low, and very low based on study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias.[13] The risk of bias for each included study was determined using the ROBINS-I tool.[33] The overall risk of bias was judged based on the individual risk of bias of the included studies.

Included Articles

The PRISMA flowchart for article selection is shown in Figure 4. A total of 345 articles were identified. All articles except those that specifically pertained to the use of IVIG and organ ischemia were excluded during the screening process. The remaining 52 abstracts were reviewed, of which 19 articles where IVIG was studied as a treatment for other neurologic disease, 4 preclinical studies, 4 existing reviews, and 1 letter were excluded.

Risk of Embolic and Ischemic Events

One study comparing serum viscosity before and after IVIG in 13 patients determined that IVIG increased serum viscosity, potentially impairing blood flow and triggering a thromboembolic event in certain patients.[7] Another study determined 3 of 7 patients with thrombotic complications received multiple IVIG infusions before suffering a

TABLE 1: Studies Included in the Review.

Authors, Publication Year	Study Design	Quality Grade	Risk of Bias	Country	Patients Receiving IVIG (n)	Patients with Stroke (n)	Patients with Cerebral Infarction (n)	Patients with MI (n)	Patients with DVT (n)	Patients with PE (n)	Patients with Multiple Embolic Events (n)	Patients with Other Embolic Events (n)
Alexandrescu et al., 2005[1]	Case report	Very low	High	USA	1	1	0	0	0	0	0	0
Caress et al., 2009[6]	Case-control	Moderate	Moderate	USA	19	12	0	3	0	1	2	0
Dalakas, 1994[7]	Uncontrolled before-and-after	Moderate	Moderate	USA	13	NA	NA	NA	NA	NA	NA	NA
Emerson et al., 2002[10]	Case report	Very low	High	USA	2	1	0	0	0	1	0	0
Fonseca et al., 2011[11]	Case report	Very low	High	Portugal	2	2	0	0	0	0	0	0
Go and Call, 2000[12]	Case report	Very low	High	USA	1	0	0	0	1	0	0	0
Jin et al., 2020[16]	Case-crossover	Moderate	Moderate	USA	NA	NA	NA	NA	NA	NA	NA	NA
Kapoor et al., 2020[18]	Retrospective cohort	Moderate	Moderate	UK	112	2	0	6	1	1	0	1
Katz et al., 2003[19]	Case report	Very low	High	USA	2	1	0	0	1	0	0	0
Kayyali et al., 2008[20]	Case report	Very low	High	USA	1	0	1	0	0	0	0	0
Lorenzana et al., 2014[21]	Case report	Very low	High	USA	1	0	1	0	0	0	0	0
Marie et al., 2006[22]	Case series	Low	High	France	46	1	0	2	2	0	1	0
Nakano et al., 2016[25]	Case report	Very low	High	Japan	2	2	0	0	0	0	0	0
Paran et al., 2005[28]	Case series	Low	High	Israel	6	0	0	0	4	0	0	2
Rungjirajittranon and Owattanapanich, 2019[30]	Case report	Very low	High	Thailand	1	1	0	0	0	0	0	0
Saeed et al., 2010[31]	Case report	Very low	High	USA	1	1	0	0	0	0	0	0
Steg and Lefkowitz, 1994[32]	Case report	Very low	High	USA	1	0	1	0	0	0	0	0
Sztajezel et al., 1999[34]	Case report	Very low	High	Switzerland	1	0	1	0	0	0	0	0
Toh et al., 2020[35]	Case report	Very low	High	Malaysia	1	1	0	0	0	0	0	0
Turner and Wills, 2000[37]	Case report	Very low	High	UK	1	0	1	0	0	0	0	0
Vucic et al., 2004[40]	Case series	Low	High	USA	7	4	0	1	1	0	0	1
White and Leonard, 2007[41]	Case report	Very low	High	USA	1	1	0	0	0	0	0	0
Yanagihashi et al., 2020[43]	Case report	Very low	High	Japan	1	0	0	0	0	0	0	1
Zaidan et al., 2003[44]	Case series	Low	High	Saudi Arabia	3	0	2	1	0	0	0	0

Abbreviations:
DVT - deep vein thrombosis; MI - myocardial infarction; n - number; IVIG - intravenous immunoglobulin; PE - pulmonary embolisms; NMDA - N-Methyl-D-aspartic acid; PCA - posterior cerebral artery.

thrombotic complication.[40] A case-control study looked at whether or not typical cardiovascular risk factors increase the risk of IVIG-related thromboembolic events. The researchers found that when 4 or more cardiovascular risk factors were present, there was a statistically significant increase in thromboembolic events.[6] A retrospective cohort study found the vascular risk factors were more common in patients with inflammatory neuropathy receiving IVIG who sustained a thromboembolic event than those who did not while IVIG administration factors did not contribute to increased risk.[18] The study concluded that IVIG may play a small but contributory role in increasing thromboembolic risk in this cohort. Another study found that arterial thrombosis occurred early after IVIG administration and was associated with older age and atherosclerotic valvular disease, while venous thrombosis occurred later and was associated with factors such as obesity and immobility that contributed to venous stasis.[28] A case-crossover study determined that patients admitted for venous thromboembolism but not acute ischemic stroke or myocardial infarction were more likely to have received IVIG during a previous admission for neurological disease.[16]

Types of Embolic and Ischemic Events

Thirteen (54.2%) studies described post-IVIG stroke, 6 (25.0%) cerebral infarction, 6 (25.0%) deep vein thrombosis, 5 (20.8%) myocardial infarction, 3 (12.5%) pulmonary embolism, 2 (8.3%) multiple embolic events, and 4 (16.7%) other embolic events. The largest series of patients with inflammatory neuropathy found a rate of thromboembolic events of 10.7%,[18] and the second largest series found a rate of 13.0%.[22] The included studies described 226 patients. Of 71 patients with ischemic or thrombotic complications, 30 (42.3%) experienced stroke; 13 (18.3%), myocardial infarction; 10 (14.1%), deep vein thrombosis; 7 (9.9%), cerebral infarction; 3 (4.2%), pulmonary embolism; 3 (4.2%), multiple embolic events; and 5 (7.0%), other embolic events, such as limb ischemia. Across all reviewed studies, IVIG-related thromboembolic events were described in patients across all age groups with and without risk factors for vascular disease.

DISCUSSION

Multiple reports of IVIG-related thrombotic or ischemic events prompted the United States Food and Drug Administration to issue a black box warning regarding this risk in 2013. The black box warning states that immunoglobulin products have a risk of thrombosis including stroke, myocardial infarction, and venous thromboembolism.[3] We report a case of bilateral posterior cerebral artery infarctions following treatment with IVIG and present a systematic review of the existing literature on embolic and ischemic complications following IVIG administration.

Our patient was a 39-year-old woman who had presented with non-specific complaints of fever, nausea, vomiting, and left-sided weakness. Given the patient's presentation from a nursing home and a recent history of multiple ill individuals at that home, one of the leading diagnoses was Guillian-Barré syndrome. This had prompted IVIG administration after which, on day 2 of treatment, the patient experienced a major neurological decline and CT revealed a right posterior cerebral artery stroke with radiographic signs of increased intracranial pressure. Our patient did not have any significant risk factors, such as underlying cardiovascular or hematologic disease, aside from hypothyroidism, but subsequently developed bilateral fatal malignant strokes beginning on day 2. Although the relationship between IVIG and increased thromboembolic risk has not been clearly elucidated and it is difficult to explain why our patient developed fatal malignant strokes following her IVIG treatment, we present additional findings from our review of the current literature to provide further context.

Embolic and Ischemic Complications

Review of the 24 included articles revealed that IVIG may be associated with a risk of embolic and ischemic complications. Our results contrast with the results of a meta-analysis of 31 randomized controlled trials in which Ammann et al. found no significant association between IVIG and thromboembolic adverse events.[2] Nonetheless, these complications are rarely reported and may be more frequent under certain conditions. Multiple IVIG infusions may raise the serum viscosity to the threshold necessary to precipitate embolic events.[40] Patients with preexisting cardiovascular risk factors may be particularly at risk of thromboembolic events.[6,18] Although IVIG appears to increase the risk of venous thromboembolism but not arterial thromboembolism,[16] whether patients sustain arterial or venous thrombotic events may depend on patient-specific factors. Patients who are older or have atherosclerotic disease are more likely to experience arterial thrombosis, whereas patients with conditions contributing to venous stasis are more likely to experience venous thrombosis.[28]

IVIG and Stroke

Although acute ischemic stroke has been documented in young patients without any vascular risk factors who were receiving IVIG therapy, there have been no definitive associations found between IVIG and increased risks of stroke. Caress et al. reported the largest series consisting of 16 occurrences of stroke after IVIG administration and found that only 50% of strokes occurred within 24 hours after IVIG administration.[5] Furthermore, Okuda et al. identified no association with the infusion rate or solution medium with which the IVIG was delivered and stroke.[26] Conversely, Widiapradja et al. and Basta claim that patients who received IVIG administration had a 4-fold decreased stroke risk than the general population.[4,42]

In addition to conflicting reports on the potential link between IVIG and increased risk for stroke, a plausible pathophysiological mechanism to explain stroke risk associated with IVIG remains controversial. Hypothetical mechanisms may involve changes in serum viscosity[7] and vasospasm after infusion,[34] hyperinflammatory[1] and hyperthrombic/hypercoagulable states[8] in ill patients. Some authors report a collective role of all the aforementioned mechanisms as playing a critical role in stroke. Alexandrescu et al. describe a quantifiable increase in serum viscosity secondary to IVIG that may be attributable to an increase in

stroke risk.[1] Dalakas also makes similar claims,[7] and both reports explain that increased serum viscosity in the setting of an acute inflammatory state secondary to dehydration, infection, trauma, or other presentation pathology could collectively pass the threshold for thrombus formation, leading to an ischemic event. Critical illness promotes a hyperinflammatory state that can lead to endothelial and vessel wall dysfunction and thrombus formation. Combined with limited mobility, longstanding muscle weakness, and strength deterioration, this environment increases the risk for vascular complications.

Limitations

This study has limitations. The case report describes a single case and is not meant to be representative of the spectrum of embolic and ischemic complications after IVIG. The systematic review is also subject to biases. Only studies reporting embolic or ischemic complications after IVIG were included, overestimating the proportion of patients receiving IVIG who sustain these complications. Included studies were at high risk of bias due to retrospective design. Included studies were primarily case reports or small case series, which are rarely representative of the typical patient. The quality of included studies was very low. No randomized controlled trials were identified. Only studies written in or translated into English were included, perhaps excluding relevant reports from other areas. Only studies with full text manuscripts were included, leading to publication bias. Studies with low rates of embolic and ischemic complications may be underreported in the literature. No meta-analysis was conducted due to heterogeneity of reports, although a statistical analysis was possible. Despite its limitations, this study presents a novel case and systematically reviews existing literature to inform clinicians regarding embolic and ischemic complications of IVIG and guide clinical practice.

CONCLUSION

Although the exact association between IVIG and risk for acute ischemic stroke has not fully been identified, stroke can be a very debilitating and potentially fatal complication in patients undergoing IVIG treatment. This highlights the need for further investigation into the vascular and cellular mechanisms of acute cerebral artery thrombosis during IVIG administration to avoid future morbidity and mortality.

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