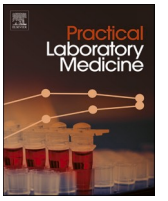
Practical Laboratory Medicine 42 (2024) e00434

Contents lists available at ScienceDirect

Practical Laboratory Medicine

journal homepage: www.elsevier.com/locate/plabm



Registered Report Stage II

Falsely abnormal serum protein electrophoresis after administration of intravenous immunoglobulins (IVIG): A retrospective cohort study

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ARTICLE INFO

Keywords:
IVIG
SPEP
MGUS
Gammopathy
False positive rate

ABSTRACT

Intravenous immunoglobulin (IVIG) therapy, used in several neurologic, hematologic, immunologic and dermatologic conditions, is known to interfere with the results of some serum laboratory tests. We analyzed the potential interference of IVIG on serum protein electrophoresis (SPEP) by reviewing more than a decade of SPEP studies performed by the clinical immunology laboratory of the Johns Hopkins Hospital. Of the total 100,350 SPEP performed between January 1, 2013 and December 31, 2023, 395 contained the keyword IVIG in the pathologist report, contributed by 348 patients confirmed to have received IVIG by chart review. Of the 348 patients, 20 (6 %) had a M-spike on SPEP suggestive of monoclonal gammopathy, while 328 (94 %) did not have it. Of the 20 patients, 14 received IVIG within 30 days from the SPEP collection date, while 6 received beyond 30 days. Serum immunofixation electrophoresis (SIFE) and clinical follow up showed no evidence of monoclonal gammopathy in 5 of the 14 patients. Overall, this 11-year retrospective cohort study showed that 5 of 348 (1.4 %) patients treated with IVIG and tested by SPEP had a false M-spike, that is a spike not confirmed to be caused by a monoclonal gammopathy by subsequent studies. Although small, the false positive rate of 1.4 % suggests that integrating knowledge of recent IVIG administration into the pathologist report would reduce SPEP misdiagnosis.

1. Introduction

Intravenous immunoglobulin (IVIG) therapy is commonly used for the treatment of autoimmune, infectious and neurological disorders. IVIG is prepared by pooling immunoglobulins from thousands of healthy blood donors. Its composition resembles that of human plasma and predominantly (>90 %), comprising IgG, smaller amounts of other immunoglobulins, and low levels of cytokines and other proteins [1].

IVIG was first approved by the FDA for the treatment of primary immunodeficiency [2]. It was then expanded to neurological diseases such Guillain-Barre syndrome, Stiff-Persons syndrome, neuromyelitis optica spectrum disorders, myasthenia gravis, and rheumatological diseases such adult dermatomyositis [2,3]. In hematological and immunological disease, IVIG is used to supplement immunoglobulin levels in patients affected by primary and secondary antibody deficiencies. The examples indicated above highlight the main uses of IVIG but do not take into account the ever-expanding list of off-label uses, such as treatment for COVID-19 for which

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https://doi.org/10.1016/j.plabm.2024.e00434
Received 1 August 2024; Received in revised form 14 September 2024; Accepted 13 October 2024
Available online 19 October 2024

Abbreviations

IVIG	Intravenous Immunoglobulin
SPEP	Serum Protein Electrophoresis
SIFE	Serum Immunofixation
MGUS:	Monoclonal gammopathy of undetermined significance
MM	Multiple Myeloma

studies have produced inconclusive results due to a cohort of factors including timing, dosage and patient complications [4,5]. While the merits of IVIG is beyond the scope of this paper, it is a therapeutic option available in hospitals within the United States of America.

The mechanisms of action of IVIG are complex and not fully understood. Intuitively, the transfer of antibodies provides immediate protection against a broad array of pathogens and toxins. This form of passive immunization is temporary (lasting only as long as the transferred immunoglobulins remain active in the recipient), but clearly effective in immunodeficient patients [6]. Besides its antibody replacement role, IVIG exerts numerous effects on cellular immunity. IVIG has been shown to inhibit the excessive activation of antigen-presenting cells and promote apoptosis in lymphocytes and monocytes, overall decreasing the inflammatory burden [7]. As reviewed by Norris et al., transferred immunoglobulins saturate and block receptors that are specific for the Fc portion of the antibodies. These receptors, called Fc receptors, comprise a family of receptors expressed on macrophages, dendritic cells, and B lymphocytes: by ligating endogenous antibodies, they mediate the effector functions of the antibodies, such as complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity. When blocked by the transferred IVIG, endogenous autoantibodies are hindered from binding to the Fc receptors, resulting in an amelioration of the autoimmune pathology [6]. Since in normal conditions antibodies have a longer effective half-life when bound to their Fc receptors, saturating these receptors with IVIG promotes the catabolism of endogenous antibodies, thus decreasing the autoimmune burden [6]. IVIG has also been found to interfere with complement deposition/fixation and modulate T-cell populations-in particular IVIG is capable of expanding the Treg population [6]. There has also been evidence supporting the IVIG possesses anti-idiotype activity against autoantibodies [8].

IVIG is not only an effective treatment but also quite tolerable. In a 10-year retrospective review of IVIG treatments, 32 % of patients experienced an adverse event but this was minor and mainly consisting of fever, rash, and/or chills (72.2 % of all symptoms). More serious events such as hemolysis, cyanosis, hypotension, hypothermia, vomiting, and chest pain were rare, and primarily attributed to fast infusion rates, thus manageable by slowing the infusion rate [9–11].

As IVIG is a pooled preparation derived from thousands of donor IgGs, it is known to affect laboratory tests that depend upon the measurement of serum antibodies. Arnold et al. demonstrated that passive transfer of anti-HBc from IVIG products led to false positives of anti-HBc serology. In the study there was a 46 % positive amongst patients screened versus the expected seroprevalence of 1 % in Canada where the study took place [12]. Such findings prompted an investigation; however, it is important to note that on an individual scale this discrepancy may not have been picked up and findings might have been overlooked. The authors conclude that these false positives can be reduced by testing patients prior to IVIG administration, 3 months or more post IVIG administration or using tested IVIG products free of anti-HBc [12]. IVIG manufacturers are aware of the potential interference and misleading results that may arise from IVIG usage and serology testing and even include a warning with the product [13].

We designed this retrospective cohort study to assess whether the administration of IVIG interferes with the interpretation of serum protein electrophoresis (SPEP) by causing the appearance of a monoclonal spike, commonly referred to as M-spike.

2. Methods

2.1. Data sources

The study used two electronic sources of medical records: the database of electrophoresis results curated by the clinical immunology laboratory of the Johns Hopkins Hospital using FileMaker (from Claris, Cupertino, CA), and the EPIC hyperspace (Verona, WI). We first searched the immunology database for SPEP studies performed during the past decade (from January 1st, 2013 to December 31, 2023) containing the keywords “IVIG” and/or “intravenous immunoglobulins” in any of the 4 fields that compose the SPEP report: description, interpretation, history, or recommendation. A study is defined as an elctrophoresis of serum proteins performed by a laboratory technician and then reviewed and interpreted by a pathologist. We classified as abnormal those studies containing the keywords “spike”, “band”, and/or “gammopathy” in the description and/or interpretation sections of the SPEP report. Clinical charts were then reviewed in EPIC hyperspace to confirm that IVIG were indeed administered and to collect information about the timing of this administration. The timing was chosen based on the average half-life of IVIG preparations [14–16], and classified as recent when IVIG were given within 30 days from the SPEP collection date or remote when given beyond 30 days. Charts were then reviewed to attribute the SPEP positive to a diagnosis of primary plasma cell disorders (MGUS, multiple myeloma, Waldenström macroglobulinemia, AL amyloidosis), B cell lymphoproliferative disorders, or secondary causes of gammopathy. Finally, the immunology database was queried again to identify whether an immunofixation electrophoresis (SIFE) had been performed on the same serum specimen, as to determine the true positive rate (positive SPEP and positive SIFE) and false positive rate (positive SPEP spike but negative SIFE) of the initial SPEP report.

Gel electrophoresis of serum proteins.

For SPEP, sera were fractionated by gel electrophoresis using the HYDRAGEL 30 thin-layer agarose system (Sebia, Lisses, France) according to the manufacturer's recommendations. Briefly, after the gel was run, stained, and scanned by a densitomer (GELSCAN, from Sebia), delimiters were placed by a technologist to bracket the 5 protein regions (albumin, alpha-1, alpha-2, beta, and gamma), as well as the presence of possible M-spikes. The SPEP, both the actual gel and its densitometric scan, was then passed on to the pathologist who, upon reviewing the patient chart, wrote a report that appeared in the patient chart. SPEP is the most used screening test for monoclonal gammopathies, typically accompanied by the measurement of serum free light chains and by a serum immunofixation electrophoresis (SIFE). The pathologist may have added a SIFE on the serum specimen where SPEP was performed, or the specimen may have already come with an order for SIFE. SIFE study is the gold standard to confirm the presence of a monoclonal spike and determine its composition in terms of immunoglobulin heavy and light chains; in this study, it was carried out using the Hydrasys 2 apparatus (also from Sebia). SPEP and SIFE studies were reported as independent tests by the pathologist, their result appearing in the patient chart at the time of verification, which was typically different between SPEP (earlier) and SIFE (later).

The study was approved by the Institutional Review Board of the Johns Hopkins Hospital (IRB00435041).

3. Results

Of the total of 100,350 SPEP performed during the study period, 395 contained the keyword IVIG (and/or intravenous immunoglobulin) in the pathologist report. SPEP studies were contributed by 353 patients, 348 of whom confirmed to have received IVIG by chart review. Patients included 219 females and 129 males, females being significantly younger (49 ± 16) than males (55 ± 18 years, $p = 0.0014$).

Of the 348 patients, 20 (6 %) had an abnormal SPEP based on the presence of the keywords "spike, band, monoclonal, and/or gammopathy " in the pathologist report. Of them, IVIG administration was recent (within 30 days from the serum collection date) in 14 patients, or remote (beyond 30 days) in the remaining 6 patients (Fig. 1).

Of the 14 patients with recent IVIG administration, 9 had a positive SIFE and a diagnosis of plasma cell dyscrasia (true positives), 1 a positive SIFE but no clinical diagnosis of plasma cell dyscrasia (false positive), and 4 a negative IFE and no diagnosis of plasma cell dyscrasia (false positives) (Fig. 1). Overall, of the total 348 patients with a history of IVIG administration noted in the SPEP report and confirmed by chart review, 5 patients, all males, had a M-spike in the SPEP that was not confirmed to be a true monoclonal gammopathy by the subsequent SIFE and diagnosis assignment, yielding a false positive rate of 1.4 %. These five patients are described in more details in the following section.

We also estimated the total false positive rate of SPEP in the study cohort (not just that due IVIG administration) by using sera where both SPEP and SIFE were performed on the same specimen number. Of the total of 100,350 SPEP in the study period, 50,572 also had a SIFE on the same blood draw. Of them, 18,159 (36 %) were reported to feature one or more M-spikes. The subsequent SIFE analysis showed that in 3106 studies there was no monoclonal band, yielding a false positive rate for SPEP of 17 % (3106 of 18,159).

Patient 1: A 82-year-old male had received a diagnosis of chronic inflammatory demyelinating polyneuropathy, and was treated with monthly IVIG for the presence of progressive numbness, weakness, and peripheral neuropathy. The SPEP study revealed no protein or globulin elevations but an asymmetrical gamma region containing a possible faint M-spike of 1.0 g/L. Serum IFE was added to the specimen and showed a faint and ill-defined band of restricted electrophoretic mobility in the cathodal region of the G and kappa lanes, thus interpreted as IgG kappa monoclonal gammopathy. IVIG was continued for 2 years but then stopped since symptoms did not improve. Imaging studies performed during follow up showed no evidence of multiple myeloma or other plasma cell dyscrasias. Additionally, there was no suspicion for Waldenström macroglobulinemia, and a sural nerve biopsy ruled out amyloidosis. A urine IFE performed 3 years after the initial SPEP was negative for gammopathy. These findings were interpreted as a false positive of both SPEP and SIFE secondary to the concurrent administration of IVIG (see Table 1).

Patient 2: A 44-year-old male had a diagnosis of MDA5 dermatomyositis predominantly involving the skin, with mild muscular

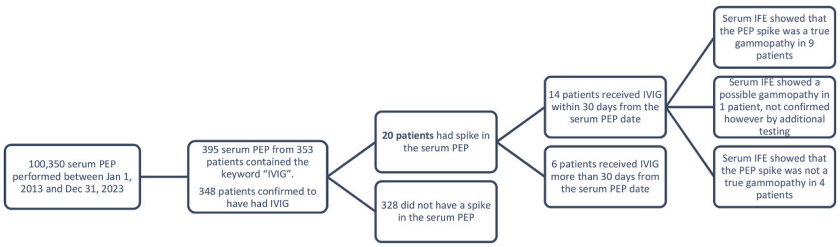

Fig. 1. Depiction of the structure of the retrospective cohort study. The clinical immunology laboratory of the Johns Hopkins Hospital was analyzed between the periods of January 1st, 2013 to December 31st, 2023. 100,350 SPEP/SIFE samples were run during this time and from them the keywords "IVIG" and/or "intravenous immunoglobulins" in any of the 4 fields that compose the pathologist report: description, interpretation, history, or recommendation. We then classified as abnormal those studies that contained the keywords "spike", "band", and/or "gammopathy" in the description and/or interpretation sections of the SPEP report. From this cohort 24 patients were found but only 15 were within the 30-day window of IVIG usage. From these patients 10 patients exhibited a true gammopathy (Positive SPEP, positive reflux SIFE and clinical diagnosis/follow up testing supportive of the results), 4 patients exhibited a false gammopathy (Positive SPEP, negative reflux SIFE) and 1 patient exhibited a false gammopathy through follow-up testing (Positive SPEP, positive reflux SIFE but follow up uIFE testing was negative).

dysfunction and no interstitial lung disease. He was being treated with IVIG every 2 weeks in conjunction with sildenafil and prednisone. SPEP showed increased total proteins (88 g/L, normal range 60–82 g/L) because of an increased gamma region (28 g/L, normal range 7–17 g/L) (Table 2). The gamma region was broad-based, thus suggesting polyclonal hypergammaglobulinemia, but also contained a faint spike, so that a SIFE was added to the study (Fig. 2A). SIFE showed polyclonal bands and no evidence of gammopathy (Fig. 2B). Similarly, uPEP showed no M-spike, only a significant mixed glomerular and tubular proteinuria. No further immunology work-up was performed on this patient.

Patient 3: A 59-year-old male was diagnosed with Guillain-Barre syndrome and treated with 5 days of IVIG. After an initial positive response, he was transferred to JHH for further management. SPEP showed elevated total protein (92 g/L) and gamma globulins (35 g/L). The gamma region contained an M-spike (8.6 g/L), so that the study was reported as consistent with a gammopathy and SIFE performed. SIFE showed no evidence of a monoclonal gammopathy. No further immunology work up was done on this patient. The

Table 1
Characteristics of IVIG treated Patients who had SPEP/SIFE testing within a 30-day window.

Patient Number	Age	Sex	Follow-Up Years	Gammopathy Present Upon SIFE Follow-Up	Follow-Up SIFE Gammopathy Type	Initial Clinical Diagnosis
1	23	M	5	No	N/A	CIDP
2	73	M	7	Yes	IgM Lambda monoclonal gammopathy	CIDP
3	63	F	8	Yes	IgM Lambda monoclonal gammopathy	Multifocal Motor Neuropathy
4	84	M	7	Yes	IgG kappa monoclonal gammopathy	CIDP
5	29	M	5	Yes	IgG kappa monoclonal gammopathy	CIDP
6	64	M	4	Yes	IgG kappa monoclonal gammopathy	Multiple Myeloma
7	74	F	3	Yes	IgM Kappa monoclonal gammopathy	CIDP
8	58	M	8	Yes	IgG kappa monoclonal gammopathy	Anti-GAD65/Variant Stiff Person Syndrome
9	84	M	4	Yes	IgG kappa monoclonal gammopathy	GBS
10	44	M	2	No	N/A	Dermatomyositis
11	59	M	1	No	N/A	GBS
12	57	M	2	No	N/A	CIDP
13	63	F	5	Yes	IgG lambda monoclonal gammopathy	Scleromyxedema
14	72	M	4	Yes	IgG Kappa and IgM lambda biclonal gammopathy	CLL
15	43	F	1	Yes	IgG kappa monoclonal gammopathy	ITP

Table 2
Serum protein electrophoresis fraction percentage and quantification in patients' 2 and 4.

Patient 2

Fraction	%	Ref %	g/L	Ref g/L
Albumin	46.3	61.0-71.0	38.9	31-54
α1	2.9	1.4-2.9	2.4	1-4
α2	8.9	7.0-11.0	7.5	4-11
β	8.9	8.0-13.0	7.5	5-12
Gamma	33	9.0-16.0	**27.7**	7-17
Total Protein			84	60-82

Patient 4

Fraction	%	Ref %	g/L	Ref g/L
Albumin	40.5	61.0-71.0	35.6	31-54
α1	3.2	1.4-2.9	2.8	1-4
α2	12	7.0-11.0	10.6	4-11
β	12.1	8.0-13.0	10.6	5-12
Gamma	32.2	9.0-16.0	**28.3**	7-17
Total Protein			88	60-82

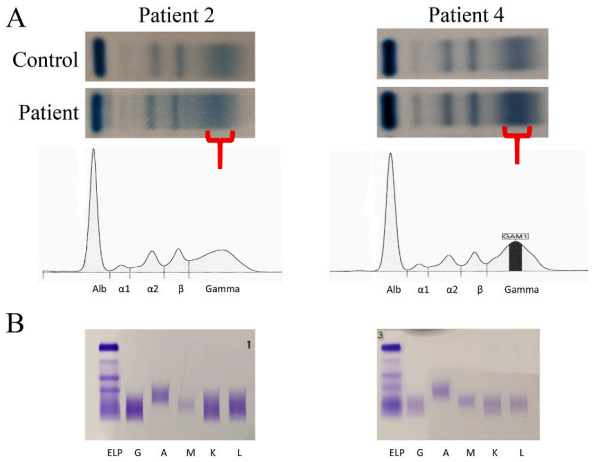

Fig. 2. Representative SPEP/SIFE results depicting false gammopathy in patients with recent IVIG usage. **(A)** SPEP results with corresponding densitometry plots of patient 2 and 4 whom both demonstrate broad peaks in the gamma regions with the presence of a potential faint spike (highlighted by red marker). **(B)** Subsequent reflux SIFE testing following SPEP results in patients 2 and 4. SIFE testing was revealed no signs of gammopathy.

patient responded well to plasmapheresis.

Patient 4: A 57-year-old male was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy characterized by symptoms of paresthesia and extremity weakness, and electromyographic features of demyelination. He was being successfully managed with IVIG treatment every 3 weeks. He was on IVIG for 3 years prior to current presentation. SPEP was ordered for a paraprotein evaluation. SPEP revealed elevated gamma globulins (28 g/L) and total proteins (84 g/L). Additionally, a broad spike was observed (1.01 g/dL) (Fig. 2A–Table 2). This was classified as a possible monoclonal gammopathy and SIFE was reflexed which showed no band of restricted electrophoretic mobility (Fig. 2B). No further immunology work up was done on this patient and he is still being managed for CIPD with the same treatment regimen.

Patient 5: A 23-year-old male was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy with symptoms of lower extremity numbness and difficulty walking. Prior nerve conduction study highlighted demyelination with motor conduction velocities in 20s–40s. He was being successfully managed with IVIG treatment every 2 weeks. SPEP was ordered revealing elevated gamma globulins (35 g/L) and total proteins (95 g/L). This was classified as a possible monoclonal gammopathy and SIFE was refluxed which showed no band of restricted electrophoretic mobility. No further immunology work up was done on this patient. Patient disease was successfully treated with IVIG, prednisone, and rituximab over a 6-year period.

4. Discussion

This retrospective cohort study highlights the correlation between recent IVIG administration (within 30 days) and serum protein electrophoresis studies featuring a M-spikes, thus suggestive of a monoclonal gammopathy. Amongst a population of 348 patients treated with IVIG and tested by SPEP, 5 had a M-spike that turned out to be not a true monoclonal spike in subseqwuent studies, thus yielding a false positive rate of 1.4 %.

SPEP is a relatively inexpensive screening test, commonly used in patients suspected to have a plasma cell dyscrasia but also in a

variety of other conditions. Like most screening tests, SPEP has a well described false positive rate averaging around 20 %. Causes are numerous. A marked polyclonal elevation in serum immunoglobulins, as seeen in patients with Sjogren syndrome, systemic lupus erythematous, and chronic viral infections can lead ato a condensation or asymmetry in the lane of the agarose gel that can be interpreted as a M-spike. Similarly, the presence of residual fibrinogen in the serum sample causes a false M-spike at the border between the beta and gamma regions, and increased concentration of transferrin gives the appearance of a spike in the beta region. More recently, the administration of monoclonal antibodies for a variety for an ever-expanding list of diseases can also impart a M-spike apperance to the SPEP that is however not caused by a plasma cell monoclonal tumor. In this study we reported that IVIG administration can also cause a false M-spike on SPEP.

Numerous studies have reported the false positive potential of IVIG usage in various serum laboratory tests, especially those based on antibodies [12,13,17,18]. To our knowledge, however, no study has correlated IVIG administration with SPEP/SIFE testing. For the diagnosis of monoclonal gammopathies, the SPEP/SIFE combination of testing is extremely reliable and has a sensitivity of 92.7 % and specificity of 96.3 % with a positive predictive value of 92.7 % and negative predictive value of 96.3 %. As such, 1.4 % is seemingly a small percentage, given the critical importance and presumptive reliability of SPEP/SIFE in the diagnosis of MGUS, Waldenstrom and Multiple Myeloma combined with the high volume of immunology lab samples run by hospital labs, addressing this issue is an important factor in reducing misdiagnosis [19].

The results in our retrospective cohort study have several limitations. The findings are correlative and aside from patient 1, the other patients did not have subsequent electrophoretic studies performed post-IVIG therapy to provide further supportive evidence. Future studies may assess patients prior to, during and post IVIG treatment for definitive results. Additionally, the screening methodology to arrive at the cohort used for analysis was based on comments in the SPEP database on IVIG usage and whether the SPEPs were abnormal which has the potential to overlook false positives in patients where the pathologist didn't note IVIG usage.

In line with our results a case report by Ruhe et al. presented a patient with IgM MGUS with nephrotic syndrome which had common variable immunodeficiency treated with IVIGs every 3–4 weeks. Renal biopsy showed membranoproliferative glomerulonephritis of the immune complex type with deposits of IgM matching the serological findings of the paraproteinemia. Bone marrow biopsy excluded Waldenström macroglobulinemia, MM and other malignancies. IVIG was discontinued and serum levels of IgM, sFLC-lambda and proteinuria dropped to the point that the patient did not fit the criteria for MGUS [17]. This report highlights similar findings to our study but has the added strength of showing patient results post discontinuation of IVIG treatment with demonstration of MGUS dissipation post-discontinuation.

As not all physicians are not aware of the potential of false positive after IVIG administration if SPEPs are ordered without proper interpretive background it may lead to misdiagnosis, extensive patient workup and unnecessary expense. We recommend that any interpretation of SPEPs with concurrent IVIG treatment (within 30 days) be interpreted with caution and to make clinical judgments in combination with clinical presentation, imaging, bone marrow biopsy, electrophoretic results and other supportive testing.

With the ever-expanding use of IVIG in patient care there should be an apparent notification in a patient's chart upon the administration or scheduled administration of IVIG which is easily observable when consulting physicians are reviewing the chart so that serum studies can be planned around therapy/interpreted with the proper context to ensure validity of results.

CRediT authorship contribution statement

Andrew Sulaiman: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Patrizio Caturegli:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis.

Ethics approval

Study was approved by the Institutional Review Board at Johns Hopkins (IRB00435041)

Funding statement

The project was support by an educational grant to Patrizio Caturegli.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplemental Information

No supplemental Information.

Data availability

Data will be made available on request.

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