Falsely Abnormal Serum Protein Electrophoresis after Administration of Intravenous Immunoglobulins (IVIG): A 10 Year Retrospective Cohort Study

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Background

IVIG is prepared by pooling immunoglobulins from thousands of healthy blood donors. Its composition resembles that of human plasma and predominantly (>90%) comprises of IgG and smaller amounts of other immunoglobulins and cytokines/proteins [1].

IVIG was first approved by the FDA for the treatment of primary immunodeficiency. Its usage was then expanded to multiple diseases including Guillain-Barre syndrome, Stiff-Persons syndrome, neuromyelitis optica spectrum disorders, myasthenia gravis, immune thrombocytopenia, multiple myeloma and chronic lymphocytic leukemia[2,3]. There is also an ever-expanding list of off-label uses, such as treatment for COVID-19.

IVIG has been found to affect laboratory tests. One such example by 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% positivity amongst patients screened versus the expected seroprevalence of 1% in Canada where the study took place [4].

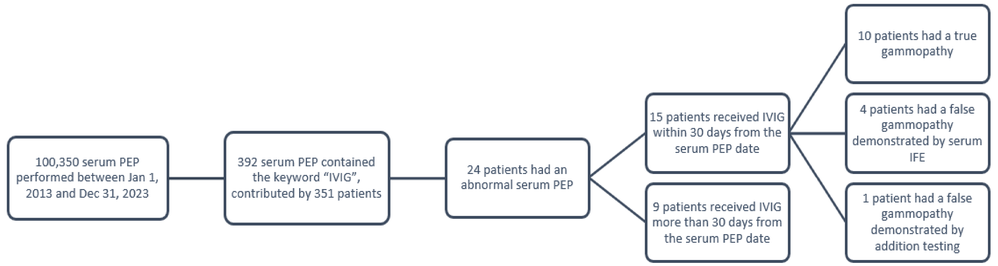
While reports have demonstrated IVIG interferences in DAT, Syphilis and HEP B no study has used a patient cohort to assess whether IVIG can affect sPEP results. Here we preformed a retrospective cohort analysis over a 10-year period to whether administration of IVIG interferes with the interpretation of serum protein electrophoresis (sPEP) by causing the appearance of a false myeloma (i.e. monoclonal) spike, commonly referred to as an M-spike. As sPEP/SIFE are the gold standard for diagnosis of a monoclonal gammopathy interference could have wide-reaching effects directly impacting patient management.

Design

The clinical immunology laboratory of the Johns Hopkins Hospital was analyzed between the periods of 01/01/2013 to 12/31/2023. 100,350 sPEP/sIFE samples were assessed and samples identified using keywords “IVIG” and/or “intravenous immunoglobulins”. We identified abnormal studies with the keywords “spike”, “band”, and/or “gammopathy” in the description and/or interpretation. Clinical charts were then reviewed to determine recent IVIG usage and the immunology database was queried on whether an immunofixation electrophoresis was performed on the selected cases, as to determine the true positivity of the sPEP spike.

Results

Figure 1 :Depiction of the Design/Findings of the retrospective cohort study



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).

Figure 2: Representative sPEP/sIFE results depicting false gammopathy in patients with recent IVIG usage

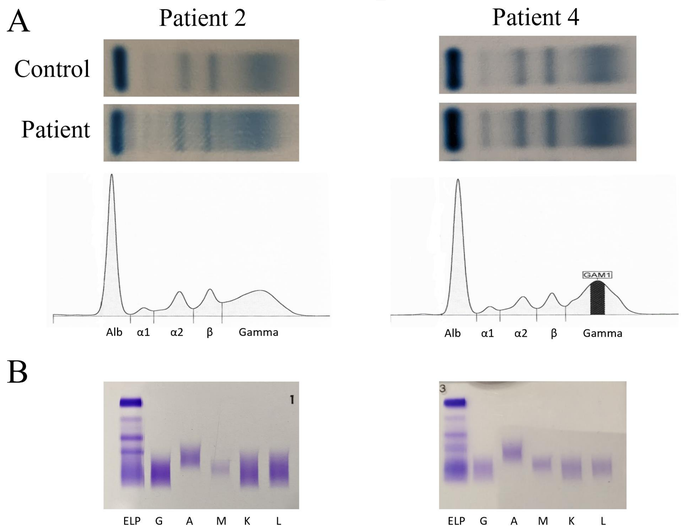


Figure 3: Serum Protein Electrophoresis Fraction Percentage and Quantification

Patient 2

Fraction	%	Ref %	g/dl	Ref g/dl
Albumin	46.3	61.0-71.0	3.89	3.10-5.40
α1	2.9	1.4-2.9	0.24	0.10-0.40
α2	8.9	7.0-11.0	0.75	0.40-1.10
β	8.9	8.0-13.0	0.75	0.50-1.20
Gamma	33	9.0-16.0	**2.77**	0.70-1.70
Total Protein			8.4	6.0-8.2

Patient 4

Fraction	%	Ref %	g/dl	Ref g/dl
Albumin	40.5	61.0-71.0	3.56	3.10-5.40
α1	3.2	1.4-2.9	0.28	0.10-0.40
α2	12	7.0-11.0	1.06	0.40-1.10
β	12.1	8.0-13.0	1.06	0.50-1.20
Gamma	32.2	9.0-16.0	**2.83**	0.70-1.70
Total Protein			8.8	6.0-8.2

Results

Figure 4: 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

Conclusion

-We found a **1.42%** false positivity rate correlated with IVIG usage.

-To our knowledge there has been no study using a patient cohort to assess the potential false positivity rate of IVIG in regards to sPEP testing.

-Given the critical importance of sPEP 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.

-We recommend that any interpretation of sPEP with concurrent IVIG treatment be interpreted with caution and are working with Chemistry/TM/Immunology to implement a notification in a patient’s chart upon IVIG administration so that serum studies can be interpreted with the proper context to ensure validity of results.

References

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