CASE REPORT

Unmasking of myasthenia gravis during pegylated Alfa 2 a interferon and ribavirin therapy for chronic hepatitis C

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Abstract

Over last few decades, hepatitis C has emerged as a serious infection that has threatened the health and budgets of millions in the world. The objective of health professionals to treat it with recommended therapy of Alfa interferon and Ribavirin combination presents certain risks. One of the alarms is the ability of interferon to stimulate the production of autoantibodies in the body resulting in expression of autoimmune diseases in few who develop these antibodies. The case presented here is about unmasking of myasthenia gravis in a patient who received alfa interferon therapy for her chronic hepatitis C. Alfa interferon probably plays an important role in manifestation of the diseases in susceptible patients and all autoimmune diseases cannot be taken as mere side effects of the therapy. Clinicians need to be alert to pick up these diseases earlier so that the prompt management is possible.

Keywords: Autoimmune diseases, Chronic active hepatitis C, Alfa interferon therapy.

Introduction

Hepatitis C is an infection that is mainly transmitted through blood to blood contact and is known to affect the liver primarily. WHO rated Pakistan second in the list of heavily affected by hepatitis C (after Egypt), with approximately 8.6 million people affected by it.[1]

It has multitude of clinical presentations: acute, sub acute and chronic infection.[2] In addition to its propensity for causing cirrhosis of liver, it also poses a risk of liver cancer. It causes paramount effect on the quality of lives of patients, as cirrhosis precludes portal hypertension with its all manifestations of bleeding varices, ascites, hepatorenal syndrome and hypersplenism.

The recommended treatment, until recently, for chronic hepatitis C is pegylated interferon and ribavirin given for a period of 6 to 12 months depending on genotype and other criteria; boceprevir, telaprevir, sofosbuvir being expensive additions to therapy in some cases.[3] Co-antiviral therapy is associated with numerous side effects.

The commonly encountered side effects are flu like symptoms, severe depression and psychosis, cytopenias, precipitation of autoimmune disorders like hypothyroidism.[4] There is increased interest in understanding the mechanisms by which this therapy might flare the autoimmune diseases. There are studies that delineate the role of Alfa interferon therapy in precipitating myasthenia gravis.[5]

There are anecdotal case reports that emphasize the causation of myasthenia by interferon therapy but this report mentions the revelation of masked myasthenia gravis interferon therapy in our patient.

Myasthenia Gravis is an autoimmune neuromuscular disease. Interferon alfa 2 a induced myasthenia gravis was first reported in 1995 in a patient treated for leukaemia.[6]

Since then, case reports have implicated interferon alfa in causing myasthenia gravis during treatment of malignancy or chronic active hepatitis C.[7-9]

We present the case of a 25 year old female in whom myasthenia gravis was unmasked by interferon therapy for hepatitis C.

Case Presentation

A 25 years old female presented with complaints of gradual onset mild weakness of her limb girdle muscles in Jan, 2013. Her weakness increased with walking and combing hair but with little diurnal variation.

There were no muscles/ joints pain, fever, photosensitivity or weakness in chewing, swallowing and talking. Her examination showed mild reduction in proximal muscles power; 4±5 with normal deep tendon reflexes, cranial nerves and rest of neurological examination.

Investigations including blood complete picture, muscle enzymes, inflammatory markers, thyroid profile, nerve conduction studies and electromyography were normal.

Anti-acetylcholine receptor antibodies were negative and so was autoimmune profile including ANA, ENA

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Table: Patient's profile during the treatment with Alfa interferon and Ribavirin.

	Side effects	TLC	HB	Platelets	ALT	Qualitative PCR for
Dec, 2013	Muscular pains	4800/mm^5	11gm/dl	188000/mm^3	41 IU/L	Negative
Feb, 2014	Headache. Anaemia	5100/mm^3	7.8gm/dl	156000/mm^3	35 IU/L	Negative
April, 2014	Joints and muscles pain	7200/mm^3	10.1gm/dl	198000/mm^3	22 IU/L	Negative

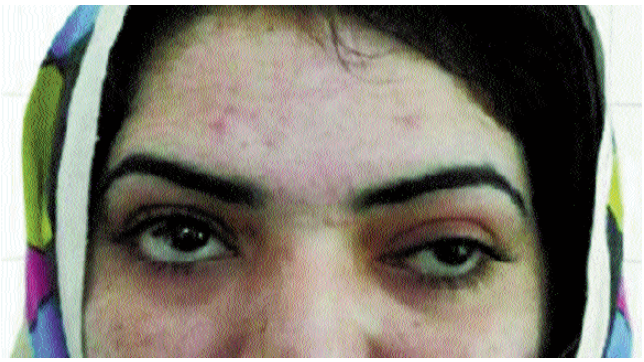

Figure: Prominent ptosis of left eye (accompanying weakness and diplopia on abduction of left eye) and adduction of right eye.

Antibodies, Anti ds DNA and RA factor.

Finding no clue for the cause of this mild muscle weakness and keeping her on sound follow-up, she was reassured and sent home. Within days she reported improved symptoms.

Later, in OPD, in Oct, 2013, she had increased serum alanine aminotransferase levels (43u/l). She reported a history of tooth extraction, her hepatitis serology by Elisa confirmed her to be positive for anti HCV abs. Quantitative PCR showed a viral load of 190000 and viral genotype of 3a.

After her detailed assessment, she was started on pegylated interferon alfa 2 a, 180 mcg, subcutaneous once a week along with Ribavirin 500 mg twice a day. She achieved a rapid virological response and developed anaemia that was managed with recombinant erythropoietin. Serum iron, folate and B12 levels were normal (Table). During 18th week of treatment, she complained of bogginess in her eyes towards the end of day and diplopia when she looked laterally with her left eye. She also experienced weakness in proximal muscles of limbs so she presented to us (after receiving her 23rd interferon injection). Her treatment was immediately stopped and she was admitted for complete evaluation and within 1 week she started complaining of difficulty and tiredness in chewing, swallowing and talking. She had bilateral ptosis more evident on left side with restriction of her right eye adduction, left eye abduction and diplopia on left eye abduction (Figure). Her single breath count test, continuous eye lids and repetitive arms raising revealed fatigability. Motor system examination showed proximal muscles power of 3/5. Gower's sign was positive. The rest of her examination was unremarkable.

At that time, her nerve conduction study was suggestive of myasthenia gravis and so was electromyography! CPK, Serum aldolase levels, thyroid function tests were normal and she had negative thyroid autoantibodies. Anti-acetylcholine receptor antibodies titre was more than 60 nmol/L (Normal: <.04nmol/L)

Based on above findings, diagnosis of myasthenia gravis unmasked by Alfa interferon therapy was made and she was started on pyridostigmine, to which she showed appreciable improvement.

CT chest showed no thymoma/thymic hyperplasia. She has achieved sustained virological response.

Discussion

Detailed chronology of this case shows that the patient's myasthenia gravis was actually 'unmasked' by the Alfa Interferon therapy. We don't see any reason to call it as 'induced' by alfa interferon therapy as almost 1 year before she was started on therapy with interferon, she had developed vague fluctuating proximal Myasthenia like weakness of her limbs. Her tendency to develop Myasthenia was potentiated by interferon and the disease manifested in a vigorous way! The underlying pathogenic mechanism might remain same in both the conditions but clinical implications differed.

The possible mechanism employed by Alfa Interferon therapy in causing myasthenia gravis is by production of autoantibodies against the acetylcholine receptors through its immunomodulatory action are the antibodies produced against nuclear and thyroid antigens and insulin.[10,11]

Not all the patients develop clinically evident autoimmune diseases but in one study where 31 patients were tested for development of different antibodies, 27 patients developed atleast one autoantibody during the treatment.

Not all who developed antibodies developed clinical disease except small minority of 'susceptible' patients.[11]

This suggest that susceptible patients should be identified by getting detailed histories (personal/ family) and required biological tests of the patients particularly for serious illnesses like myasthenia gravis and before initiating the treatment of hepatitis C.

Not much of the case reports described before clearly mentioned about the past medical histories of patients which were significant for any myasthenia like symptoms or even for any other autoimmune diseases associated with myasthenia (SLE/Rheumatoid arthritis/Pernicious anaemia).

A disease caused by Interferon can be incidental, if it is unmasked by interferon, it can be deferred by proper evaluation and pre treatment of the patients with the new oral drugs.

Conclusion

Our patient had a non specific weakness of her proximal limb girdle muscles about year before diagnosis of chronic active hepatitis C. She improved by herself until she received combined antiviral therapy, when her weakness got manifested: clinically and serologically favouring the diagnosis of myasthenia gravis. This proved the immunostimulatory effect of interferon.

It is suggested that physicians should be alert before and during treatments with Alfa interferon therapy. Patients need to be educated about side effects and early reporting to their physicians particularly in underdeveloped countries so that prompt management can be ensured.

Conflict of interest: The author doesn't declare any conflict of interest

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying image.

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