ABSTRACT

Guillain-Barre syndrome (GBS) is usually a monophasic illness but relapses occur. A 55-year-old female with hypertension and vitiligo presented with acute inflammatory demyelinating polyradiculoneuropathy. She improved with immunoglobulin treatment started on day 6 of illness, but relapsed on day 14 warranting repeat immunoglobulin therapy. Thereafter recovery was complete. Her relapse was due to treatment-related fluctuation (TRF). TRF is improvement in the GBS disability scale of at least one grade after completion of immunotherapy followed by worsening of the disability scale of at least one grade within the first 2 months after disease onset. Recurrent GBS and chronic inflammatory demyelinating polyradiculoneuropathy were excluded. During the peak of the illness ANA titres were transiently high. The presence of other medical conditions, predominant proximal weakness and the absence of preceding diarrhea are predictors for TRF seen in this patient. Early treatment and evidence of ongoing immune activation have contributed toward TRF.

Key words: Relapse of Guillain-Barre syndrome, recurrent Guillain-Barre syndrome, treatment-related fluctuation

Introduction

Guillain-Barre syndrome (GBS) is usually a monophasic illness, but relapses due to recurrences and treatment-related fluctuations (TRF) with immunotherapy (immunoglobulins or plasma exchange) do occur. TRF needs to be differentiated from acute onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP). The following describes such a case of TRF and its predictors.

Case Report

A 55-year-old female who suffered from vitiligo and essential hypertension came to the Neurology unit with progressive weakness of the lower limbs over 5 days. She had flaccid motor weakness (proximal>distal) and areflexia with intact sensation. Over the next 2 days her weakness ascended to involve the upper limbs. Acute Inflammatory Demyelinating Polyradiculoneuropathy was confirmed by electrophysiological studies. Intravenous Immunoglobulin was initiated on day 6 of the illness and continued for 5 days. On day 7 she had Grade 2 power in the lower limbs and Grade 4 power in the upper limbs (GBS motor disability scale of Grade 3). She made gradual recovery until day 13, when she had Grade 4 power in the lower limbs and normal power in the upper limbs. She was able to walk without assistance (Motor disability of Grade 2). Subsequently she deteriorated with increasing weakness which was ascending. By day 16 she was quadriplegic (Grade 0 in lower limbs, Grade 2 in upper limbs) and she could not flex her neck (Motor disability of Grade 4). The vital capacity decreased to 800 ml. A repeat nerve conduction study showed worsening neuropathy. She was hyponatremic (108 meq/l) suggesting Syndrome of Inappropriate Secretion of AntiDiuretic Hormone. There were fluctuations in the blood pressure and heart rate reflecting autonomic involvement. Cerebrospinal fluid analysis at this juncture demonstrated cytoprotein dissociation. Treatment with intravenous immunoglobulin was recommenced and continued for 5 days. The hyponatremia was managed with fluid restriction. On Day 25 she was able to walk without support (lower
limbs-Grade 4) and was subsequently discharged (Motor disability scale of Grade 2).

Investigations during her stay in hospital including full blood count, ESR, CRP, renal and liver functions were normal. The ANA titre during the peak of the illness was 1/320. Autoimmune screen and screening for HIV, Mycoplasma, Campylobacter, Cytomegalovirus and HSV were negative. Clinical evaluation and investigations had ruled out associated connective tissue disorders, malignancy and chronic infections. She made a complete recovery. Repeat nerve conduction at 6 months of follow-up also showed complete recovery. The ANA had come down to 1/40.

Discussion

The clinical evolution of this patient’s GBS fits with the definition of TRF. TRF is defined as improvement in the GBS disability scale of at least one grade after completion of immunotherapy (immunoglobulin/plasmapharesis) followed by a worsening of the disability scale of at least one grade within the first 2 months after disease onset.[2,3]

Recurrence of GBS is identified and is defined as two or more episodes that fulfilled the criteria for GBS, with either a minimum interval greater than 4 months between episodes if the patient did not recover completely or greater than 2 months when there was a complete or near-complete recovery after the previous episode.[2] The above patient did not fit the criterion for a recurrence.

The differential diagnosis of TRF to be considered is A-CIDP. Thus differentiating the two entities are paramount. The diagnosis of A-CIDP should be considered when a patient thought to have Guillain-Barre syndrome deteriorates again after 8 weeks from onset or when deterioration occurs three times or more.[2,4,5] In a Dutch study 10% of 170 subjects diagnosed with GBS had TRF, and all of the episodes occurred within 8 weeks after symptom onset, typically at around 4 weeks after onset. Median length of time before the first TRF was 18 days, (ranged from 10 to 54 days); 31% had a second TRF, but no additional fluctuations after 8 weeks. None of the eight patients found to have A-CIDP began fluctuating until after 8 weeks in the said study. The above patient deteriorated within 8 weeks of onset of illness (day 16) and has not shown a consecutive chronic course but had complete recovery by 6 months without any further deterioration making A-CIDP an unlikely diagnosis. In the Dutch study A-CIDP patients were less severely affected, did not need artificial ventilation and rarely had cranial nerve dysfunction which makes A-CIDP in our patient unlikely as she showed greater disability, keeping with the diagnosis of GBS-TRF.

Many attributes of the above patient act as predictors of TRF. Romano et al suggested the presence of an associated medical condition as a predictor of relapse.[6] Our patient had vitiligo and also hypertension. A Dutch study concluded that the most important factor for not having TRF was the presence of predominant distal weakness.[3] Our patient had predominantly proximal weakness. Also preceding diarrhoea, presence of anti-GM1 antibodies were associated with the absence of TRF.[3] There was no preceding diarrhea in the above patient as well. Presence of sensory signs and cranial nerve involvement had a positive association with TRF.[3] However, this was not seen in our patient.

The above patient experienced a rapid deterioration in muscle strength with neck and respiratory muscle involvement. In the Dutch study GBS-TRF patients were more severely affected when compared to patients with GBS without fluctuations.[3]

TRF may occur in two circumstances. If therapy is initiated very early when the disease process is active, it will only temporarily arrest the disease process and once treatment is over the disease could recur.[7] In such instances repeat treatment improves the outcome as seen in our patient.

Immune reactions against target epitopes in Schwann-cell surface membrane or myelin result in acute inflammatory demyelinating polyradiculoneuropathy; reactions against epitopes contained in the axonal membrane cause the acute axonal forms of GBS.[8] The predominant mechanisms by which IVIg therapy exerts its action appear to be a combined effect of complement inactivation, neutralisation of antibodies, cytokine inhibition and saturation of Fc receptors on macrophages.[9] Fluctuation with early relapse and improvement on repeat treatment thus could be thought as due to rebounding of the antibodies or immune reactions on those epitopes. However, some studies dispute this claim.[8] In one description of a Japanese man with TRF the antibody titres steadily declined irrespective of the clinical fluctuations and authors concluded that the clinical fluctuation was not due to changes in the production of antibodies but presumably due to the inflammatory response in peripheral nerves outlasting the transient beneficial effects of intravenous immunoglobulin.[10]

Recurrence may also be due to ongoing immune activation.[3] A transient high ANA titre and the presence
of vitiligo seen in this patient may signify autoimmunity as an underlying mechanism for the TRF. Therefore early treatment, and continued immune activation could have contributed to the TRF in our patient.

Conclusions

This case illustrates the value of insight regarding the risk factors for TRF for the practicing clinician to give a reasonable prognosis and to anticipate and be prepared for difficulties in management. Also there is a need to rule out other coexisting immune disorders and to exclude A-CIDP as an alternative diagnosis.

References