Normal Pressure Hydrocephalus Associated with Chronic Alpha Interferon Treatment: A Case Report

Siret RATİP*, Tülin BUDAK-ALPDOĞAN*, Önder ALPDOĞAN*, Mustafa ÇETİNER*, Sami KARTI*, İlhan ELMACI**, Mahmut BAYIK*

* Department of Hematology, Marmara University Hospital, İstanbul, TURKEY
** Department of Neurosurgery, Marmara University Hospital, İstanbul, TURKEY

ABSTRACT

Chronic a-interferon use has been reported to cause a variety of neurotoxic side effects. This case summary suggests the possibility of a new neurotoxic side effect of normal pressure hydrocephalus following chronic a-interferon use.

Key Words: Alpha interferon, Normal pressure hydrocephalus.

Turk J Haematol 2000;17(1):33-35.

INTRODUCTION

Alpha interferon has been increasingly employed in the treatment of haematological disorders. During the last decade it has become the mainstay of therapy in the management of patients with chronic myeloid leukemia (CML) who lack a matched sibling donor for allogeneic bone marrow transplantation[1]. The most common reason for termination of a-interferon treatment is its various side effects, which become intolerable for some patients[2]. Neurotoxic side effects are common in chronic a-interferon therapy, and include somnolence, confusion, psychiatric symptoms, conceptual disorganisation, neurological deficits, cortical blindness, seizures, vertigo, occulomotor nerve paralysis, distal paraesthesia and peripheral neuropathy[2,3]. So far, there have been no reports of disorders of cerebrospinal fluid circulation, such as normal pressure hydrocephalus (NPH) caused by a-interferon use. NPH is characterized by ventricular dilatation, but normal CSF pressure. It classically presents with a triad of gait disturbance, urinary incontinence and dementia. The causes and pathophysiology of idiopathic NPH remain poorly understood, and no definable cause can be identified in the majority of cases[4]. The prevalence of systemic hypertension is increased in NPH,

but the reason for this is unknown[5]. A number of cases are associated with a preceeding history of subarachnoid haemorrhage, head trauma, tumour, radiation, meningitis, Paget disease of the bone of the skull, mucopolysaccharidesis of the meninges, or achondroplasia. Here we report a case of NPH associated with chronic a-interferon use.

CASE REPORT

A 62 year old housewife, who presented with lethargy, was diagnosed to have CML. She was Philadelphia chromosome positive, and at presentation the leucocyte count was 126.000/mm^3, Hb was 11.8 g/dL and platelet count was 293.000/mm^3. Hydroxyurea was commenced, but despite increasing its dose, the leucocyte count remained elevated at 52.900/mm^3 one month after the diagnosis. Alpha-interferon was added at this stage at a daily dose of 5.000.000 U subcutaneously. A combination of hydroxyurea and a-interferon, successfully reduced the leucocyte count allowing a gradual reduction in the dose of hydroxyurea, which was stopped after 3 months of therapy when the leucocyte count was reduced to 6.500/mm^3. Treatment was continued with a-interferon only. The patient remained in haematological remission, but not in cytogenetic remission as she was found to have only a minimal cytogenetic response at the 6 month check up. Considering that she was in haematological remission, the dose of a-interferon was not increased to greater than 5.000.000 U daily.

The patient had been noted to have hypertension at her initial examination when she presented with CML. No secondary causes of hypertension, such as renal disease, could be identified and she was commenced on a combination of cilazapril and hydrochlorothiazide one month prior to the start of a-interferon therapy. However, satisfactory control of hypertension could not be achieved and the regime was changed to diltiazem 9 months following the commencement of a-interferon. It was initially felt that a-interferon might have been responsible for failure to control hypertension, but when control was achieved with diltiazem no changes were made to a-interferon therapy. Diltiazem had to be changed to verapamil 4 months later, as the patient found it easier to comply with a one tablet daily regime. Hypertension remained under satisfactory control afterwards.

The patient presented with a two day history of nausea, vomiting, and drowsiness 13 months following the diagnosis of CML, and 12 months after the commencement of a-interferon. The neurological examination was normal. However, as her symptoms were severe, she was admitted by the neurology department for investigation and observation. A differential diagnosis of vertebrobasilar insufficiency, subdural haematoma, and vestibulitis was suggested. MRI scan revealed calcification in the vertebrobasilar system, mild enlargement of the 3rd ventricle and frontal horns of the lateral ventricles. The calcification of the vertebrobasilar system was not severe enough to cause vertebrobasilar insufficiency. NPH was also not suspected at this stage, and mild enlargement of the ventricles were felt to be age related. Her symptoms gradually resolved during the next 8 days, and neurologists felt that a diagnosis of vestibulitis causing these symptoms was most likely. Therefore, she was not followed up further at the neurology clinic and no MRI scan follow up was requested after discharge from the hospital. Considering she was in haematological remission, and as there was uncertainty about whether a-interferon was responsible for this transient complaint, a-interferon therapy was not stopped. No other side effects related to a-interferon use had been observed until this stage with the possible exception of the initial failure to control hypertension. She remained asymptomatic during her monthly haematology follow up visits with no further symptoms of nausea, vomiting, or drowsiness. However, she again complained of drowsiness and mild nausea during her routine visit 8 months following the initial presentation. A repeat MRI scan of the brain at this stage revealed marked dilatation of the third ventricle and the lateral ventricles. No obstruction to the Silvian Aquaduct was observed. A lumbar puncture revealed a normal CSF pressure, and hence a diagnosis of normal pressure hydrocephalus was made. As her symptoms had progressively deteriorated, a decision for a ventriculo-peritoneal shunt was taken by the neurosurgeons. Unfortunately, she had an incidence of aspiration pneumonia on the 4th post-

operative day, rapidly followed by respiratory arrest, cardiac arrest, and death.

DISCUSSION

Neurotoxic side effects of a-interferon are known to be more common in elderly patients, following intramuscular or intravenous administration, and at higher doses of frequent injections of a-interferon[3]. Our case had the risk factors of being elderly and having freguent injections. She had no other side effects related to a-interferon use with the possible exception of the initial failure to control hypertension. She gave the warnings of a neurological problem 8 months prior to the definitive diagnosis of NPH, but a near normal brain MRI scan and a resolution of her symptoms after nearly one week prevented us from suspecting a side effect by a-interferon, which had been effective in the control of her CML. The second presentation was severe enough to require the insertion of a ventriculo-peritoneal shunt within days, and the possibility of a reversal of the NPH upon withdrawal of a-interferon could not be explored. It is therefore possible that the finding of NPH in this patient is coincidental. However, with the knowledge of other drugs leading to disorders of cerebrospinal fluid circulation and brain oedema, such as case reports of tetracycline, danazol, glucocorticoids, ciprofloxacin and amphortericin B leading to benign intracranial hypertension[6], physicians should be alert to the possibility that other drugs lead to similar problems.

In conclusion, patients with central nervous system neurotoxicity following a-interferon use should be explored with an MRI scan and physicians should be alert to the possibility of NPH.

REFERENCES

1. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-a therapy. Ann Inter Med 1995;122:254-61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. Drug Saf 1994;10:115-50.
3. Merimsky O, Chaitchik S. Neurotoxicity of interferon-alpha. Anticancer Drugs 1992;3:567-70.
4. Mori M, Mima T. To what extent has the pathophysiology of normal-pressure hydrocephalus been clarified? Critical Reviews in Neurosurgery 1998;8:232-43.
5. Krauss JK, Regel JP, Vach W, Droste DW, Borremans JJ, Mergner T. Vascular risk factors and arteriosclerotic disease in idiopathic normal-pressure hydrocephalus of the elderly. Stroke 1996;27:24-9.
6. Parker JR, Parker JC. Pseudotumor cerebri: A review. Ann Clin Lab Sci 1993;23:325-8.

Address for Correspondence:

Siret RATİP, MD

Department of Hematology,

Marmara University Hospital,

Altunizade, 81190, İstanbul, TURKEY