CASE REPORT

Nephrotic Syndrome in a Multiple Sclerosis Patient Treated with Interferon β1a

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ABSTRACT: ***Background:*** Interferon β has become standard therapy for reducing relapse frequency in relapsing/remitting Multiple Sclerosis (RRMS). Several different preparations are available including interferon β1a (Avonex, Rebif) and interferon β1b (Betaferon/Betaseron). For the most part these preparations have been considered safe. Recently there have been concerns relating to liver[1] and now kidney toxicity. ***Case Report:*** We present a case of a 28-yr old male who developed a severe case of nephrotic syndrome while being treated for relapsing/remitting Multiple Sclerosis (RRMS) with weekly injections of interferon β1a. ***Subsequent course:*** The nephrosis resolved almost completely once the interferon was stopped and after immunosuppressive treatment. At its peak the daily protein loss was 35.82 g. Kidney biopsy demonstrated membranous glomerulonephritis. ***Discussion:*** Two other case reports of nephrotic syndrome have been reported in the literature. This latest (third) report suggests that the safety profile should be reexamined and at least raises the question of potential renal toxicity of interferons in MS.

RÉSUMÉ: Syndrome néphritique chez un patient atteint de sclérose en plaques traité par l'interféron β1a. ***Introduction:*** L'interféron b est devenu le traitement standard pour diminuer la fréquence des récidives dans la sclérose en plaques récurrente/rémittente (SEPRR). Plusieurs préparations différentes sont disponibles dont l'interféron β1a (Avonex, Rebif) et l'interféron β1b (Betaferon/Betaseron). En général, on considérait que ces préparations étaient sûres. Depuis peu, on s'inquiète de leur toxicité hépatique et maintenant de leur toxicité rénale. ***Observation:*** Nous rapportons le cas d'un patient de 28 ans, originaire des Émirats arabes unis, qui a développé un syndrome néphritique aigu au cours du traitement de sa SEPRR au moyen d'injections hebdomadaires d'interféron b1a. ***Suivi:*** La néphrose a presque complètement disparu suite à l'arrêt du traitement et à un traitement immunosuppresseur. En phase aiguë, la perte quotidienne de protéines était de 35,82 g. La biopsie rénale a montré qu'il s'agissait d'une glomérulonéphrite membraneuse. ***Discussion:*** Deux autres cas de syndrome néphritique ont été rapportés dans la littérature. Ce troisième cas indique que le profil de sécurité des interférons devrait être réexaminé et soulève des questions concernant leur toxicité rénale chez les patients atteints de la SEP.

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Interferon β has become standard therapy for relapsing/remitting Multiple Sclerosis (RRMS) both in North America and in Europe.[2,3] Three preparations are available. Interferon β1b is distributed as Betaseron in North America and Betaferon in Europe and the Middle East. Interferon β1a is available worldwide as Avonex, given weekly as an intramuscular injection, and Rebif, which is given three times a week subcutaneously.

The drugs are generally well-tolerated but side effects are common and include injection site reactions and flu-like symptoms.[4] Laboratory abnormalities are described and most commonly are lymphopenia, neutropenia, and raised liver transaminases.

More recently there have been reports of more serious complications arising in the context of interferon therapy. It was initially thought that changes in liver enzymes were not serious and were reversible. Recently there have been reports of serious liver disease with three cases severe enough to require liver transplantation.[5] The mechanism of liver disease in patients taking interferons may be autoimmune hepatitis. There are many other reports of autoimmune disease occurring during interferon therapy. These include myasthenia gravis, hyper- and

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hypothyroidism, Raynauds phenomenon and rheumatoid arthritis.[6] Capillary leak syndrome resulting in death has been reported in the German literature.[7] This may also have been on the basis of an immunological basis.

Reports of kidney disease arising in patients with Multiple Sclerosis (MS) on interferon therapy have been rare with only two previous cases reported.[8,9]

Case report

This patient first presented with neurological disease in 1996 at the age of 20. He complained then of headache, dizziness, ataxia and left arm/leg weakness. Magnetic resonance imaging (MRI) of the brain showed multiple lesions typical of demyelination in the corpus callosum, periventricular white matter, and brainstem. He was treated with iv methylprednisolone and recovered.

His next major attack was in June 2002 with blurred vision in the left eye, nystagmus and a spastic ataxic gait. A diagnosis of multiple sclerosis was made and he was started on interferon β1a, 30mcg weekly. Over the next two years he remained well with a residual reduction in visual acuity to 20/50, mild endpoint tremor on finger-nose testing and mild ataxia on heel to toe walking.

In April of 2004 he presented to Shaikh Khalifa Medical Centre with a three-week history of swollen legs as far as his thighs and presacral area. Initial evaluation revealed massive tissue edema but otherwise normal general physical examination with stable temperature and vital signs. Laboratory investigations showed normal hematology, thyroid function, hepatitis screen, blood chemistry (except serum protein of 42 g/l and albumen of 17 g/l), liver enzymes and complement studies. Rheumatoid factor, antinuclear antigens, C-ANCA, P-ANCA and anti-double-stranded DNA antibodies were all normal. Specifically his serum creatinine was 88μmol/l and BUN 6.0 mmol/l. A 24hr protein collection quantitated proteinuria at 21.54 gm/24hr and creatinine clearance of 94 ml/min. Urinalysis showed 30 WBCs/cm^3, 20 RBCs and no casts. Urine protein electrophoresis showed unselective protein loss. Renal ultrasound showed normal appearing kidneys measuring 11.4 (R) and 11.5 (L) cm.

The patient was a sergeant in the police force in Abu Dhabi, married with two children. He had been previously well other than his neurological disease and a remote appendectomy. Family history was negative for both neurological and renal disease. Medications had been restricted to interferon, and for two weeks, lasix, the latter prescribed for his leg swelling.

The renal diagnosis was of massive nephrosis and interferon was stopped. Lasix was continued and his nephrotic syndrome monitored over the subsequent weeks.

Stopping the interferon was insufficient to control his renal disease. There was an initial improvement in his proteinuria from 21.54 g/24hrs to 14.18 g/24hrs followed by an exacerbation reaching 35.82 g/24hrs by the 22nd of May 2004. He was admitted to hospital for pulse steroid therapy and kidney biopsy. He was given 1 g methylprednisolone iv daily for three days. Renal biopsy showed stage two membranous nephropathy with clear "spikes" apparent on Jones silver stain. Thickened glomerular basement membranes were evident with focal increase in the mesangial matrix. A few glomeruli showed segmental sclerosis, and there was mild interstitial fibrosis. The vessels appeared unremarkable. No subendothelial or mesangial deposits were identified. No tubuloreticular inclusion bodies were seen.

Post iv therapy he was continued on oral methylprednisolone at 48 mg/day. Mycophenolate, 500 mg bid, and cyclosporine, 100 mg q12h, were added on June 6th. Prindopril, 4 mg od, was added on June 21st and he required a two week course of oral nystatin for steroid induced oral thrush on August 30th. On his current management of oral steroids (methylprednisolone 16 mg/day), and cyclosporine, 100 mg q12h, he has improved with loss of weight, improved serum proteins and a reduced proteinuria of 1.12 g/24hrs (December 2004). Serum creatinine peaked at 139 μmol/l on 27th of May and then stabilized at 84 μmol/l.

Discussion

This case represents the third case of nephrotic syndrome in a patient with MS who was being treated with interferon β. The first case was a 52-yr-old female with MS developing nephrotic syndrome after four months of interferon, β1a therapy (three times weekly). She had a significant past history of ischemic heart disease requiring bypass surgery and treatment for congestive cardiac failure. Her proteinuria was 4.6 g/24hrs. Kidney biopsy showed mild focal segmental glomerulosclerosis. When interferons were withdrawn her proteinuria resolved without further intervention. The second case was a 39-yr-old man with RRMS who developed nephrotic syndrome after 22 months of interferon, β1a therapy (weekly, intramuscularly). He was otherwise well. The proteinuria was 6.7 g/24 hrs. Kidney biopsy showed minimal disease changes. Oral prednisone therapy was started and the renal disease resolved in six weeks. He relapsed in eight months and remitted again on a combination of steroids and azothioprine.

It is not known at this time whether this relationship is by chance, related to the interferon therapy, related to the MS, or related to the combination of interferon therapy and MS. The published literature to date on the association of nephrotic syndrome in MS patients untreated with interferons is sparse.[10-12] There is, however, a relationship of other autoimmune diseases occurring in MS such as myasthenia gravis.[13-14] Cases have been reported both before interferon therapy was introduced and while interferons were being used. There are associations between other interferons such as interferon α and autoimmune disease and in particular myasthenia gravis. Interferons as injected proteins are immunogenic and the common occurrence of neutralizing antibodies has been well described. It is possible then that interferon therapy in susceptible individuals induces an immune reaction that results in nephrosis. Unfortunately the varied renal biopsy findings in the three cases do not allow a precise pathogenetic mechanism.

The cases described vary in severity both in terms of initial presentation and response to therapy. This case represents severe nephrosis requiring prolonged immunosuppressive therapy. All cases have improved; one spontaneously, when interferon was withdrawn, one rapidly only to relapse, and this case responding well after three months of intensive immunosuppression.

Against a causal relationship between the use of interferons and renal disease is the lack of a consistent response to withdrawal of the drug, no consistent pathologies on biopsy, varied time intervals between onset of drug therapy and renal disease and the lack of any known subclinical toxicity such as mild proteinuria on screening. It should also be noted that only three cases of kidney disease have been described despite large

numbers of treated patients over the last 15 years. Of all the interferons used, the one used in this case is the least immunogenic.

In all three cases interferons have been withdrawn. There has been no exacerbation of the MS reported and, in this case, to date, the neurological status has remained stable. This may have been related to the continued immunosuppression used to treat the renal disease. Physicians treating MS patients with interferons are advised to be vigilant and be aware of potential renal complications.

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