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Case Report

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Cerebellitis due to Antituberculosis Therapy in a Patient with Chronic Renal Failure

Meliha TAN[1], Özlem ALKAN[a2], Sibel KARACA[1], Başak KARAKURUM GÖKSEL[1], Yusuf Ziya DEMİROĞLU[3]

[1]*Başkent Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, ADANA, Türkiye*

[2]*Başkent Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, ADANA, Türkiye*

[3]*Başkent Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları Anabilim Dalı, ADANA, Türkiye*

ABSTRACT

The incidence of tuberculosis in patients treated with hemodialysis for chronic renal failure is higher than in the general population. Further, those patients often experience adverse effects from therapy with anti-tuberculosis drugs. Although the ototoxicity and toxic retinopathy caused by anti-tuberculosis drugs is well known, the cerebellar syndrome is rare. We presented a 50-year-old woman developed cerebellar ataxia who was on hemodialysis program and taking anti-tuberculosis drugs combination therapy. Brain magnetic resonance imaging showed cerebellar edema. Cerebellar signs partially reversed after discontinuation of anti-tuberculosis therapy and initiation of pyridoxine therapy. In our patient, isoniazid was probably the drug that caused cerebellar signs and symptoms. In conclusion, a diagnosis of isoniazid-induced cerebellitis should be considered when cerebellar signs develop in patients undergoing hemodialysis and treated with isoniazid.

Key words: *Chronic renal failure, isoniazid, cerebellitis, Magnetic Resonance Imaging*

ÖZET

Kronik Renal Yetmezlikli Bir Olguda Antitüberküloz Tedaviye Bağlı Serebellit Gelişimi

Kronik böbrek yetmezlik nedeniyle diyalize giren olgularda tüberküloz insidansı normal popülasyona göre artmıştır. Ayrıca bu olgularda antitüberküloz ilaçların yan etkileri daha fazla görülür. Ototoksite ve toksik retinopati antitüberküloz ilaçların iyi bilinen yan etkileri olmasına rağmen, serebellar sendrom nadiren karşımıza çıkar. Biz bu sunumda, antitüberküloz tedavi sırasında serebellar ataksi gelişen ve kronik böbrek yetmezliği olan 50 yaşında kadın olgunun bulgularını tartıştık. Beyin manyetik rezonans görüntülenmesinde serebellar ödem saptandı. Antitüberküloz ilaç tedavisinin kesilmesi ve piridoksin tedavisinin başlamasıyla serebellar bulgularda kısmen düzelme izlendi. Bizim hastamızdaki serebellar bulgular olasılıkla izoniazid toksitesine sekonder gelişti. Sonuç olarak, izoniazid tedavisi alan diyalize giren olgularda serebellar bulgular geliştiğinde, izoniazid toksitesine bağlı serebellit tanısı akılda tutulmalıdır.

Anahtar Sözcükler: *Kronik renal yetmezlik, izoniazid, serebellit, Manyetik Rezonans Görüntüleme*

The incidence of tuberculosis (TB) in patients with chronic renal failure (CRF) is reported to be 10-fold greater than that in the general population, possibly because of decreased cellular immunity in those patients (1, 2). The treatment of TB in patients with CRF may be complicated by an increased risk of toxicity from anti-tuberculosis drugs. Ototoxicity, optic neuritis, and central and/or peripheral neurotoxic effects are well-known adverse effects of treatment with streptomycin, ethambutol, and isoniazid (INH) (3). However, there are rare reports of cerebellar syndrome caused by anti-tuberculosis drugs (1, 4, 5). We presented a patient with CRF whose cerebellar ataxia was caused by anti-tuberculosis drug therapy and the probable role of INH in cerebellar inflammation was discussed.

CASE REPORT

A 50-year-old woman with CRF caused by hypertensive nephropathy had been undergoing hemodialysis 3 times per week for 10 months. She complained of fever and moderate malaise of 1 month's duration. In general examination there were palpable cervical lymph nodes.

Cmputerized tomography (CT) of neck revealed some cervical lymph nodes enlargement. The results of cervical lymph node biopsy indicated tuberculosis lymphadenitis. Thorax CT was normal. The patient was treated with a combination of 5 antituberculosis drugs: pyrazinamide 2500 mg/d, INH 300 mg/d, rifampicin 600 mg/d, and ethambutol 1500 mg/d administered 3 times per week after each hemodialysis treatment, and streptomycin 1g 3 times per week administered 6 to 8 hours before each hemodialysis treatment. Because she experienced hearing and visual loss 2 weeks after the initiation of anti-tuberculosis treatment, therapy with ethambutol and streptomycin was terminated. At that stage, the MR imaging showed no abnormality in the cerebellum and

[a] Corresponding Adress: Dr. Özlem ALKAN, Başkent Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, ADANA, Türkiye

* 10. EFNS Congress, Glasgow, UK, 2006 ve 27. Ulusal Radyoloji Kongresi, Antalya,Türkiye 2006'da poster bildiri olarak sunulmuştur.

e-mail: yalinozlem@hotmail.com

hepatic function tests (aspartat and alanin transaminase) were in normal ranges. Therapy was continued with INH, rifampicin, and pyrazinamide. Two months later, she exhibited a mild intentional tremor and severe truncal ataxia, and she could not stand, sit, or walk without help. The results of motor and sensorial examinations were within normal limits, and no pathologic reflexes were noted. Results of the patient's cerebrospinal fluid (CSF) analysis revealed a mild elevated protein and a glucose level within the normal range. The results of testing for infectious diseases and cultures of the CSF were also within normal limits. Brain MR imaging showed diffuse cortical hyperintensity in both cerebellar hemispheres and vermis (Figure 1a, b). Anti-tuberculosis therapy was terminated, and treatment with pyridoxine 100 mg/d was initiated. Five months after discharge, a neurologic examination revealed mild ataxia with hearing and visual disturbance. In the follow-up brain MR examinations, cerebellar hyperintensity was persisting on the FLAIR and T2-weighted images.

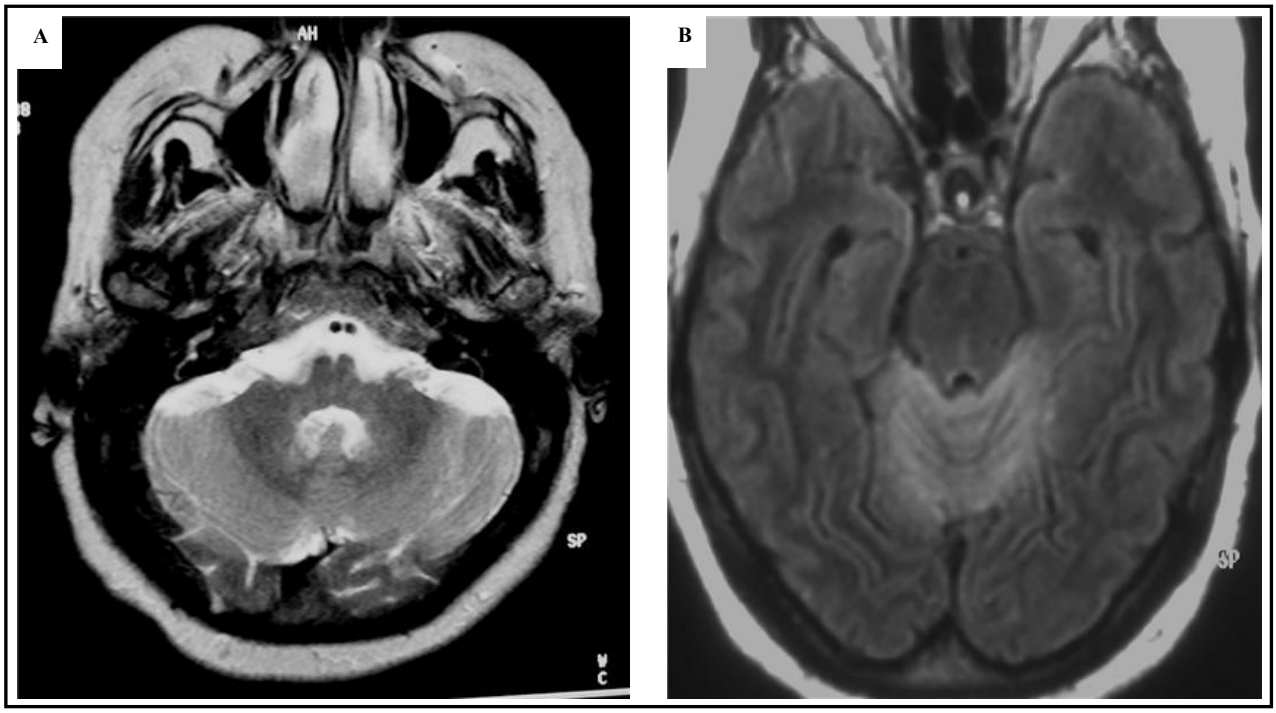

Figure 1. *Axial T2 (a) and FLAIR (b) weighted images show diffuse cortical increased signal intensity and swelling in both cerebellar hemispheres and vermis.*

DISCUSSION

A high incidence of side-effects associated with anti-tuberculosis drug treatment in patients with CRF has been reported. As the incidence of TB is increased in these patients, it is expected to encounter side effects of anti-tuberculosis drugs more frequently in this patient population. Moreover, renal failure can increase the tendency to the occurrence of side effects of drugs. The neurotoxic effects of INH are well known, ranging from peripheral neuropathy, encephalopathy, and seizure to psychiatric disorders (1-5). In the literature, only a few of hemodialysis patient was reported to suffer from INH induced cerebellar syndrome (1, 4, 5). Blumberg and Gil published a report of reversible INH -associated cerebellar dysfunction in a patient with CRF. In that case, cerebellar toxicity was completely reversed after giving pyridoxine and reducing the INH dosage (5). Siskind et al described ataxia caused by INH toxicity in 2 patients with end-stage renal disease (1). Those authors observed that INH toxicity tended to occur in patients receiving pyridoxine supplements of less than 100 mg/d, and they recommended 100 mg/d of pyridoxine supplementation for hemodialysis-treated patients who require INH. However, Cheung et al reported 3 hemodialysis-treated patients in whom INH - induced encephalopathy developed despite prophylactic pyridoxine (4). While the beneficial effect of pyridoxine on peripheral neuritis has been established, its role in prevention or treatment of INH induced encephalopathy is less certain (4). In our patient, cerebellar signs partially reversed after the discontinuation of treatment with INH, pyrazinamide, and rifampicin and the initiation of pyridoxine therapy.

Although It was well known hepatotoxicity of INH, pyrazinamide and riphampicine, only INH was reported related to neurotoxicity (6). For this reason, the cerebellar signs of presented patient must be depended on INH.

Isoniazid induces neurotoxicity by inhibiting the phosphorylation of pyridoxine, which results in the decreased production of pyridoxal-5-phosphate, a coenzyme involved in multiple metabolic functions including neurotransmission via gamma-aminobutyric acid (GABA) (7). Because GABA is the primary inhibitory neurotransmitter produced by cerebellar Purkinje cells, it

may be important in patients with cerebellar signs caused by INH toxicity (5).

It is likely that the increased incidence of INH toxicity in dialysis patients is multifactorial. In these patients, INH toxicity is attributed to malnutrition, pyridoxine deficiency, a reduced degradation rate resulting from slow acetylation, and poor renal clearance of INH (5). Our patient was well nourished, but her acetylation status was unknown.

Drug- induced cerebellitis is primarily a clinical diagnosis made by the exclusion of other metabolic or infective causes. The close temporal relationship between the onset of cerebellar findings and the initiation of drug therapy and resolution of symptoms after stopping the drug provide strong support for such a diagnosis (4). Differentiating cerebellar edema caused by drug toxicity from acute cerebellitis is difficult in MR studies. Acute cerebellitis occur as a primary infectious, post-infectious or post-vaccination disorder and mostly presents in early childhood. The most common MR imaging findings in patients with acute cerebellitis are diffuse cerebellar gray-and-white matter hyperintense signals on T2-weighted images. The CSF examination may be normal or reveal pleocytosis. Clinical improvement generally precedes that demonstrated on MR imaging. Considerable clinical improvement is shown in the course of time, whereas the MR findings persist. Cerebellar atrophy is seen in the chronic phase of the disease (8). Because our 50-year-old patient's clinical findings gradually diminished after the administration of pyridoxine and the discontinuation of isoniasid, her cerebellar signs were attributed to treatment with INH.

In conclusion, a diagnosis of isoniazid -induced cerebellit should be considered when cerebellar signs develop in patients undergoing hemodialysis and treatment with INH. The recognition of that disorder is important because complete or partial recovery is possible after discontinuation of anti-tuberculosis therapy and initiation of pyridoxine therapy.

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