Use of urokinase in the treatment of tuberculous meningitis hydrocephalus

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ABSTRACT

نستعرض في هذا التقرير حالة مريضة تعاني من استسقاء الدماغ بعد الإصابة بالتهاب السحايا التدرني (TBM)، والذي تمت معالجة حالتها بنجاح بعقار يوروكيناس. حضرت المريضة إلى المستشفى وهي تعاني من أعراض متعددة، الصداع، ارتفاع في درجة الحرارة، وقيئ. خضعت المريضة لعملية تصريف للبطين (EVD) وتمت معالجتها بعقار يوروكيناس، بالإضافة إلى عقار ديكساميثازون، وعقار اسيتازولاميد كأدوية مضادة للدرن. تم تقييم حالة المريضة سريرياً، مخبرياً، وإشعاعياً. استمرت متابعة المريضة لمدة ثلاثة أشهر، لم تعاني خلالها من أية أعراض بعد تلقيها العلاج. أظهرت الأشعة بالرنين المغناطيسي للدماغ وجود انخفاض في حجم البطين. وعليه، يمكننا اعتبار عقار يوروكيناس علاج آمن وواعد لاستسقاء الدماغ الناجم عن التهاب السحايا التدرني (TBM).

We present a patient with hydrocephalus after tuberculous meningitis successfully treated with urokinase. She presented with multiple episodes of headache, fever, and vomiting. She underwent external ventricular drainage and was treated with urokinase in addition to dexamethasone, acetazolamide, and 4 antituberculous drugs. She was evaluated clinically, radiologically, and by laboratory work-up. On short-term clinical follow-up (3 months), she was asymptomatic after the treatment with urokinase. She was radiologically evaluated 3 weeks after the treatment. An MRI of the brain showed a decrease in ventricular size. Urokinase can be considered as a safe and promising adjunctive treatment for tuberculous meningitis hydrocephalus.

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Tuberculous meningitis hydrocephalus (TBMH) is still one of the common surgical conditions that challenge neurosurgeons in developing countries owing to the controversies in its management. A very high mortality among those admitted in the late stage (in stupor or coma with or without neurological deficit) has been experienced universally. Conservative treatment affecting the outcome in such cases has still not been identified. Worldwide, 0.5-2% of patients with systemic tuberculosis present with tuberculous meningitis (TBM),[1] and TBM is the most frequent cause of hydrocephalus.[2] The current treatment for tuberculosis has a high clinical efficacy rate,[3] however, it frequently results in different degrees of residual inflammatory exudates that can obstruct the flow of CSF and cause hydrocephalus.[4] In patients with TBM, the propensity of CSF to form spiders web clots on standing, which give the reactions of fibrin, combined with the fibrinous nature of the exudate, has led to the consideration of other forms of therapy that might have a lytic action on fibrin in cerebrospinal pathways.[5] Urokinase is primarily involved in cell surface proteolysis and may play an important pathophysiological role in bacterial meningitis.[6] Intrathecal fibrinolytic agents might shorten the course of treatment and render chemotherapy more effective. We report one patient with TBMH treated by urokinase followed by remarkably good outcome and believe that urokinase can be recommended as a standard adjunctive treatment for TBMH.

Case Report. A 15-year-old girl was admitted to the hospital because of a recurring headache, fever, vomiting, and loss of weight. The girl had been well until 10 days earlier, when a headache developed that was worse when she was standing up. It became more severe over the next few days, and fever and vomiting developed. She was treated with penicillin and levofloxacin. Twenty days after the onset of symptoms, she came to the emergency department of this hospital. Her temperature was 39.8°C. A lumbar puncture was performed and the test showed protein 1.28 g/L (normal range [NR] 0.15-0.45 g/L), glucose 1.25 mmol/L (NR

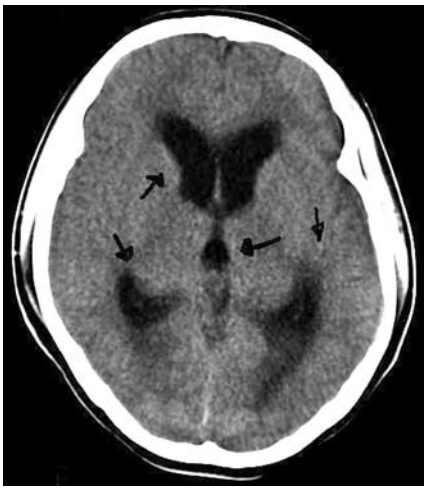

Figure 1 - Post antituberculosis therapy and before initiation of urokinase therapy CT scan shows basal meningeal enhancement and hydrocephalus.

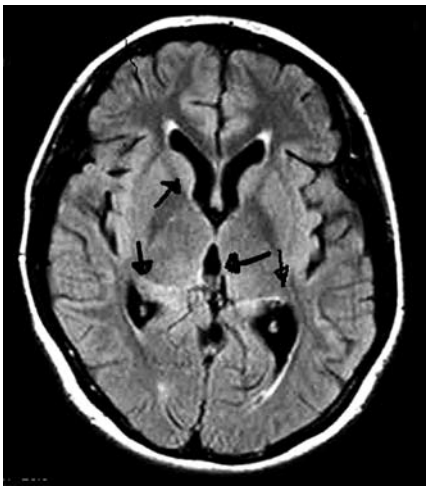

Figure 2 - After initiation of urokinase therapy, MRI shows normal sized ventricular system.

2.5-4.5 mmol/L), chloride 129 mg/dl, total cell counts 320×10^6/L, and white cell counts 302×10^6/L (NR $<10\text{x}10^6$/L). Cytological examination in CSF showed neutrophile granulocyte 0.69, lymphocyte 0.31, and acid-fast bacilli negative. The pressure of CSF was 220 mm H_2O (NR 50-180 mmH_20). She was admitted to the hospital because meningitis was suspected. The results of CT of the head and sinus area, and the chest radiograph were normal. The levels of electrolytes, the results of kidney, and liver-function tests, and the levels of total protein and albumin were normal. Blood cultures and cultures of CSF, and serologic analyses were negative. A presumptive diagnosis of TB meningitis was made, and she was initially treated with isoniazid 0.3 g, rifampicin 0.45 g, pyrazinamide 0.75 g, ethambutol 1.0 g per day and intrathecally isoniazid 0.1 g twice a week. The headache gradually resolved, and the antibiotic

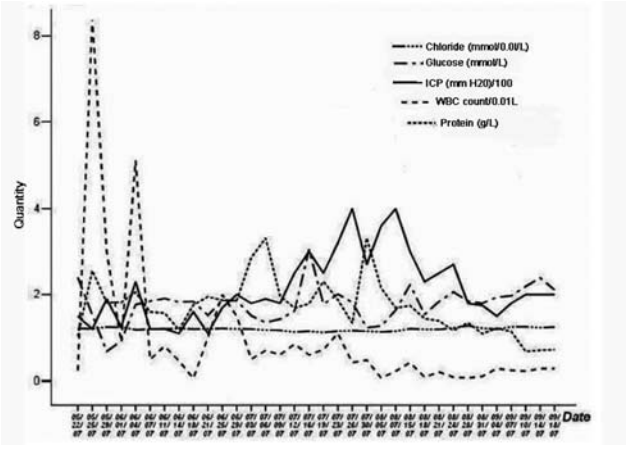

Figure 3 - Changes of intracranial pressure (ICP), protein, glucose, chloride, and white blood cell count (WBC).

treatment was continued. Four weeks later, the headache and low-grade fever recurred. A CT scan of the head was performed and showed basal meningeal enhancement and hydrocephalus (**Figure 1**). The results of routine chemistry studies were normal. The 4 drugs therapy was continued in addition to 0.5 acetazolamide twice per day to reduce secretion of CSF. The symptoms again improved. Two weeks later, 9 weeks after onset of current episode, her condition deteriorated with recurrent headache that had worsened over time, was associated with vomiting, and she lost consciousness. The temperature was 38.6°C, the heart rate 68 beats per minute, and the blood pressure 130/82 mm Hg; the findings on physical examination and laboratory tests were unchanged from those of the previous ones. External ventricular drainage (EVD) was performed. The intracranial pressure (ICP) was over 400 mm H_2O. One hour after placement of the catheter, she recovered from coma, and was followed by progressive improvement; she received intrathecal regiment with dexamethasone 2 mg and isoniazid 0.1 g twice a week in addition to 4-drug antitubercular therapy. However, after 4 days of EVD, there was relapse of headache and mental dullness and a CT scan was repeated showing the same degree of hydrocephalus. The EVD was not blocked. Intrathecal urokinase 5000U was added. During the period of EVD, the route of administration of urokinase was by lateral ventricle, and after removal of the EVD, the route of administration of urokinase was by lumbar puncture. The quantity of CSF drained by EVD increased. She had gradual clinical improvement. One week later, the persisting catheter was removed and lumber puncture was performed sequentially twice per week to withdraw 50-60 ml CSF each time. Five weeks later after the coma, the result of the MRI of the head showed normal size of ventricular systems (**Figure 2**) and

she was discharged. During her hospital stay lumbar puncture was performed 34 times. The ICP, protein, glucose, chloride, and white cell count in CSF were assayed each time (**Figure 3**).

Discussion. Tuberculous meningitis hydrocephalus is a common complication of TBM, especially in developing countries. Various modalities of treatment are available, including conservative treatment with dehydrants, external shunt, and EVD with or without external shunt. In the last few years, there have been a few reports showing the effectiveness of EVD in TBMH.[7] Our case report shows that the treatment of TBMH with EVD plus intrathecal urokinase leads to better outcome than treatment with EVD. Hydrocephalus is a relatively frequent complication in cases of TBM.[7] To reduce the severe inflammatory reaction that patients with TBM experience, past studies have administered corticosteroids.[6,8] Such a treatment, however, failed to treat hydrocephalus in our patient. Dexamethasone was used, and the patient received tuberculosis medical treatment in addition to EVD. Urokinase has also been used to try to reduce hydrocephalus. Urokinase activates plasminogen, converting it into plasmin, a non-specific proteolytic enzyme. Plasmin is capable of degrading fibrinogen and fibrin clots,[9] thus facilitating drainage of CSF. We found 2 studies conducted by Cathie,[10,11] on TBM in which intrathecal fibrinolytic agents were added to prevent the development of hydrocephalus by preventing and treating the blockage of the cerebrospinal pathways. The prevention and removal of the exudate in TBM might shorten the course of treatment and render chemotherapy more effective.[5] Another important variable that was assessed in this patient was the use of intrathecal fibrinolytic agents in the amount of fluid that can be drained. Our findings show that the patient after treatment with urokinase drained more CSF fluid than before treatment with urokinase. Since in our patient the quantity of fluid drained was greater after treatment with urokinase, we believe this was due to the effect of the urokinase, which produced lysis of the fibrin.

In our case report, urokinase as an adjunctive therapy was shown to be successful in the management of TBMH. Urokinase can be considered an ideal, safe, and promising treatment for TBMH. Therefore, we believe that administration of urokinase in patients TBMH is to be recommended.

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