CASE REPORT

Ciprofloxacin-associated posterior reversible encephalopathy

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SUMMARY

Posterior reversible encephalopathy syndrome (PRES) is a clinico-neuroradiological syndrome characterised by numerous symptoms and of no specific aetiology. Headache, confusion, seizures, cortical visual disturbances or blindness are the key symptoms. As this syndrome is reversible and readily treated by interrupting or discontinuing the aetiology, it should sharply be acknowledged. Ciprofloxacin was associated with PRES in an adolescent male treated from chest infection. It was managed in a hospital intensive care unit and was observed until disappearance.

BACKGROUND

Unwanted side effects of some drugs are not well studied by some clinicians. Thinking about the dangerous aetiologies and consequences needs to consider also the simplest rule of drug-related causes. Quinolone group drugs are very effective, yet they need greater care.

The clinical entity of reversible posterior leukoencephalopathy syndrome which is known as posterior reversible encephalopathy syndrome (PRES) was described by Hinchey *et al* in 1966. It mostly involves the loss of cerebral autoregulation and endothelial dysfunction,¹ but the pathogenesis of PRES remains debatable. This syndrome, pathognomonic lesions on MRI, consists of oedema of the subcortical white matter of the posterior cerebral hemispheres, mainly the parieto-occipital regions as shown on T2-weighted images and fluid attenuation inversion recovery images.^{2 3} The deviations occur mostly in regions vascularised by the posterior circulation, such as the posterior temporal, parietal and occipital areas. Besides, basal ganglia, cerebellar hemispheres and the brainstem may also be affected by the PRES. Seizures, headaches, altered levels of mental status and the cortical blindness are the central clinical structures of this unusual syndrome.¹

Other conditions and entities have been identified as aetiological or risk factors in the absence of hypertension (HTN), such as use of immunosuppressant drugs, sepsis and systemic lupus erythematosus (SLE),^{4 5} because most cases are due to systemic HTN. There are many other unknown causes too,^{6 7} but there are other published causes such as pre-eclampsia/eclampsia, uraemia, porphyria, neurotoxicity of cyclosporine A and a variety of other drugs.

CASE PRESENTATION

This patient was a 16-year-old non-smoker adolescent boy. An attachment of cough and wheezy

chest was reported by him and it was interpreted as chest infection (scattered wheezes and rhonchi with few crackles on right base), so initially antibiotics and expectorants were begun. He was hospitalised because the condition was not decided, hence plain x-ray was done and sputum was sent for culture. After all, a localised pneumonia was diagnosed and the most thoughtful agent in the sputum culture was reported as ciprofloxacin—one of the quinolone products. This drug is one of the recently included groups in many of the infective conditions for its wide coverage of various organisms. Sinus tachycardia, otherwise S1 and S2, was shown normal in the cardiovascular system. Abdomen was seen soft and lax. Palpable masses were not noticed. No organomegaly was found.

He developed diffuse headache on the third day and it then became localised to the parieto-occipital areas. CT of the thorax revealed palliative lower lobes consolidation with mild pleural effusion. There was neither history of hypertension nor any elevation of blood pressure. As he was not a user of eyeglasses, and also did not have major disorders causing headache, a simple analgesia was suggested. The patient was re-admitted to the hospital for further examinations. He developed dizziness, drowsiness and dyspnoea. He finally developed generalised tonic-clonic seizures (grandmal epileptic fits) with the development of agitation during wait times for different consultation to clarify the clinical condition. He was transferred to the intensive-care unit (ICU), after the administration of intravenous diazepam 10 mg and haldol, where the fits was stopped.

There were vital presence of marked dyspnoea and revealed tachycardia. In spite of the normal blood pressure for all the time which was measured of 110/55, he developed hypertension in the ICU and he received Perindopril 5 mg daily, the BP came under control gradually and nicely. Cardiac action was rhythmic at 110 bpm and the abdomen was flat and easy with upright peristalsis. Fits occurred again in the ICU despite the control of blood pressure. Full neurological examination showed non-specific findings and the patient was receptive to painful stimuli, capable of making simple movements, restless, suffering and complained of headache. There was some neck stiffness and cervicalgia. There was irregular breathing and endotracheal intubation was done with oxygen therapy under ventilation.

INVESTIGATIONS

Cerebrospinal fluid (CSF) sample was withdrawn for the possibility of meningitis. Blood samples

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were taken for full blood picture and electrolytes, and MRI was also requested. The patient was kept up on intravenous Midazolam. The blood examinations' outcomes were normal, with the exception of white blood cell (WBC) (13 000), pH 7.475, Potassium 2.7 mEq/l and creatine kinase 402 UI/l. CSF was clear and both the microbiological and chemical results were standard. Fundus examination showed normal retina. An electroencephalographic examination showed no seizure activity. MRI showed 'A T2 hyper intensity sited in the posterior cerebellar and bilaterally in the occipital region'. No intracranial haemorrhage or masses was found. There were areas of altered signal in the cortical and subcortical bilateral occipital and left cerebellar regions. Despite the absence of marked hypertension, this picture was pathognomonic for PRES findings (figure 1).

DIFFERENTIAL DIAGNOSIS

Cerebrovascular stroke, granmal epileptic fits, increased intracranial tension and meningitis were thought about. In-depth analytical review of the patient's file was completed to find any relation between findings and the MRI picture. Normal CSF excluded some of the possibilities. There was non-significant medical history. Re-evaluation was completed for drug histories by checking any possible complication or interaction. One thing was found to be related to the possible CNS manifestations even after taking the first dose and this was ciprofloxacin (Cipro) as one of the fluoroquinolones group. All of them may induce dizziness, restlessness, confusion, tremors and seizures. It is also notable that the children less than 18 years of age have a higher chance of getting bone, joint or tendon (musculoskeletal) problems such as pain or swelling while taking Cipro. It was written that Cipro should not be used as the first choice of antibiotic medicine in children under 18 years of age. As it was the only possibility that might be related to the clinical picture, Cipro was stopped and antibiotics were replaced by the fourth generation cephalosporin.

Figure 1 MRI of the brain with T2 hyperintensity sited in the posterior cerebellar and in the occipital region with the signs of vasogenic oedema.

TREATMENT

As Diazepam 10 mg and Haldol were given intravenously to stop the fits in the ICU and maintenance on midazolam was used. Also, luckily, the anxiety of restlessness decreased and respiration happening to improve after giving cephalosporins instead of cipro. On the third day, the drug was stopped and the respiration became normal, and weaning was completed from intubation and midazolam. There was no recurrence of fits and chest began to recover. For follow-up, the case was transferred to his room.

With a further treatment of 4 days of intravenous fluids, he became almost normal, but he had residual chest infection. Another brain MRI showed resolution of the previous lesions with minimal changes (figure 2). Oral cephalosporins were given and the patient was discharged. Home therapy comprised of Phenytoin 100 mg orally every 8 h for 4 weeks, Pantoprazole 40 mg orally once daily for 2 weeks, Calcium carbonate 600 mg orally twice daily for 7 days and Panadol 1 g orally three times daily as required. He was advised to be re-evaluated after two weeks.

OUTCOME AND FOLLOW-UP

The clinical condition showed progressive improvement at home with no recurrence of fits, cervicalgia or fever. After two weeks, the case came again for MRI, where no residual brain lesions were seen (figure 3 A,B). The case was advised to come after one year for re-evaluation or if there were any of the symptoms similar to the starting ones in the previous times. He was given a card to never use quinolone group drugs.

DISCUSSION

PRES can be diagnosed with reversible hyperintensities on T2-weighted cranial MR-images,^{3 8 9} as it is a complex multifactorial syndrome. The clinical distinguishing features were headache, confusion, seizures, cortical visual disturbances, blindness and other neurological signs. The posterior circulation zone was largely affected by it. The specific and exact pathogenic mechanisms most important to the development of PRES were not identified. However, regardless of the triggering factor, PRES indulged the development of oedema in the affected areas of the brain.¹⁰⁻¹²

Figure 2 MRI of the brain with an almost nearly complete resolution of the previous lesions with some minimal changes on the right side.

Figure 3 (A B) MRI of the brain with complete resolution of the previous lesions.

We have three theories for PRES. The original theory suggested, “Overreaction of brain auto regulation results in reversible vasospasm, which in turn results in potentially reversible ischemia to the brain, especially in vascular border zone territories”.²

The second theory suggested that “Auto regulation maintains a constant blood flow to the brain, despite systemic blood pressure alterations, by means of arteriolar constriction and dilatation”. Thus, the constricted arterioles are forced to dilate because of the increased systemic blood pressure, resulting in brain hyper perfusion. This increased perfusion pressure which was sufficient to overcome the blood–brain barrier, allowing extravasion of fluid, macromolecules and even red blood cells into the brain parenchyma. Thus, PRES represented vasogenic rather than cytotoxic oedema in the majority of cases.⁸

The third and the last theory suggested that at intravascular pressures just below those that could rupture the capillary wall, permeability through the endothelium increased markedly, which was most likely due to the increased pinocytotic activity through the capillary wall. The active passage of fluid through the capillary wall may act to relieve intravascular pressure,

forestalling the development of large haemorrhages.¹³ Thus, in this case, PRES was not a case in point of cytotoxic or vasogenic oedema, but it was a hydrostatic oedema. Nevertheless, the pathogenesis was endorsed to a failure of cerebral auto regulation that was possibly facilitated in posterior brain regions due to a sparse sympathetic innervation of the vertebrobasilar vascular system.¹³ However, PRES was reported in a hypertensive case associated with non-steroidal anti-inflammatory drug (NSAIDs) misuse resulting in symptoms of altered mental function, visual loss, stupor and seizures as a manifestation of acute encephalopathy and was treated by stopping NSAIDs and regulating the hypertension.¹⁴

Theories were advocated for this solid drug–disease relation, including drug-induced HTN, nephrotoxicity, direct neurotoxicity and endothelial damage.^{15 16}

Two mechanisms show that sepsis and septic shock also seemed to have a role in the pathogenesis of PRES: endothelial derangement and microcirculation disturbances.¹⁷ Similarly, bacterial and viral infections may have a role as trigger factors rather than aetiological in the pathogenesis of PRES even when sepsis or septic shock had not been established.¹⁸ To avoid the risk of irreversible lesions, the treatment of patients with PRES should be in progress as soon as it was known. However, in the management or withdrawal of the triggering factor,¹⁹ the treatment was actually based on them.

As there was neither hypertension nor any metabolic or blood changes, the aetiology of PRES in this patient remained unclear. Nevertheless, it should be related to a pharmacotoxic reason (ciprofloxacin side effects), respiratory problems continued during its intake in the ICU and clinical condition resolved after its stoppage because indications happening to develop after its intake.

According to the information of the authors, relation between Ciprofloxacin and PRES was not published elsewhere. Only central nervous system manifestations were available without referring to the PRES as a separate syndrome. A complete search was made in the literature regarding our locality in the Gulf, and no relevant cases of PRES were documented, issued or published on the subject. It is confirmed from maximum sources that this is the first publication about Ciprofloxacin associated PRES from Saudi Arabia.

Learning points

- ▶ Posterior reversible encephalopathy syndrome (PRES) is a multifactorial syndrome that should be recognised promptly because the alleged causative agent or condition was readily treated and controlled since it is reversible.
- ▶ There is a need of the accurately consoled and monitored usage of flouroquinolones drugs and other drugs with central nervous system (CNS) adverse effects, to detect early confusion or headache which may attract the clinician’s attention for hospitalisation.
- ▶ Stoppage of the cipro whenever suspected and proceeding to an urgent MRI is also mandatory at this stage to exclude major causes.
- ▶ By doing this, we can escape the full picture of PRES. If it happens, at least it can be well handled.

Competing interests None.

Patient consent Obtained.

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