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PERSISTENT HICCUPS DUE TO TUBERCULOUS MENINGITIS IN RURAL TANZANIA – THE VALUE OF XPERT TESTING IN SAMPLES OTHER THAN SPUTUM
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PERSISTENT HICCUPS DUE TO TUBERCULOUS MENINGITIS IN RURAL TANZANIA – THE VALUE OF XPERT TESTING IN SAMPLES OTHER THAN SPUTUM

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ABSTRACT

Tuberculous meningitis is the most severe form of extra-pulmonary tuberculosis and it has been associated with high mortality and morbidity. Clinical presentation of tuberculous meningitis varies, and the microbiological confirmation is usually difficult. We present two cases presented with persistent hiccups, miliary tuberculosis and tuberculous meningitis proven by positive Xpert® MTB/RIF assay in the cerebral spinal fluid. The first case improved after two weeks of treatment and completed treatment as an outpatient. The second case was discharged after three weeks of treatment after his condition improved and we learned from the relatives he died two weeks later at home.

BACKGROUND

Tuberculosis (TB) is still the number one killer infectious disease worldwide alongside HIV/AIDS. During the year 2014 it was estimated that 9.6 million people suffered from TB worldwide and among them 1.5 million died because of the related complications (1). Tanzania is considered as one of the countries with high burden of Tuberculosis globally. Together with HIV/AIDS its incidence rate is approximately to be 120 cases /100,000 inhabitants (1). Tuberculous Meningitis (TBM) is the most devastating complication of infection with Mycobacterium tuberculosis with a high morbidity and mortality, especially when diagnosis is delayed (2). Microbial confirmation of TBM is difficult, hence most of the time diagnosis is based on high index of clinical suspicion (3). We are presenting two cases from rural Tanzania with TBM confirmed by Xpert® MTB/RIF in CSF presenting with hiccups, altered mental status and fever.

CASE I PRESENTATION

A 44 years old male patient was admitted at the St. Francis Referral Hospital, Ifakara, Tanzania with a history of persistent hiccups, dry cough and fevers for three weeks without evidence of night sweats. Eight days prior to admission he developed confusion, which was mainly characterized by confabulation and mutistic episodes. Furthermore, his relatives reported a progressive weight loss for almost two months prior to the onset of the current disease.

On admission, the patient was disoriented, with a blood pressure (BP) of 121/82 mmHg. Pulse rate (PR) was 89 beats/minute, respiratory rate (RR) 22 breaths/minute, oxygen saturation 98% and body temperature 38.1°C. No focal neurologic deficits were present, Kerning and Brudzinski signs were negative. On respiratory examination, bilateral bronchial breath sounds over all lung zones were audible. General lymphadenopathy with soft, matted and non-tender lymph nodes, the largest one measuring 1.5 cm, were palpated. The rest of physical examination was unremarkable.

INVESTIGATIONS

In lumbar puncture, CSF was clear, glucose level was 3.5 mmol/L (serum glucose 6.1 mmol/L), Pandy's test for proteins was positive, and the white blood cells count (WBC) was 250 cells/μL with lymphocytic pleocytosis of 60%. Smear microscopy of CSF was negative for acid fast bacilli (AFB). Xpert® MTB/ RIF detected M. tuberculosis without rifampicin resistance. Gram staining did not reveal other bacteria. A chest X-ray revealed micronodular opacities distributed throughout both lungs (figure 1) leading to the diagnosis of miliary tuberculosis. An abdominal ultrasound was normal. The patient tested negative for HIV (rapid test, Alere, Waltham, USA); Venereal Disease Research Laboratory (VDRL), and blood slide for malaria were negative. Haemoglobin was 12.5 g/ dl, White Blood Cells (WBC) were 10.7x 109/L and platelets were 413x 103/μL. Alanine aminotransferase (ALT) level was 27.94 IU/l, aspartate aminotransferase (AST) 32.36 IU/l and serum creatinine 78 μmol/l. (Table 1).

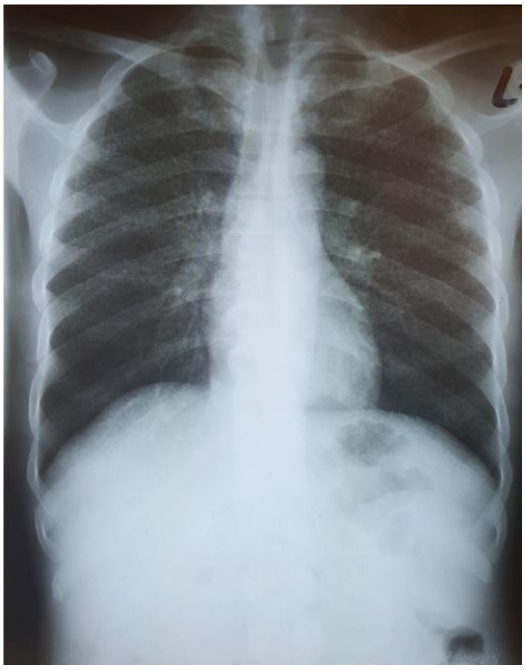

Figure 1: Posterior-anterior chest x rays of the first patient showing uniformly distributed micro-nodules involving both lungs

Table 1

Summary of clinical presentation, treatment and outcome of both patients

	Case I	**Case II**
Clinical presentation	Persistent hiccups altered mental status fever	Persistent hiccups altered mental status fever
Laboratory Blood tests –		
Full blood picture		
· Haemoglobin	12.5 g/dl	10.5 g/dl
· WBC	10.7x 10^9/L	6.7 x 10^9/L
· Platelets	413x 10^3/μL	380 10^3/μL
Creatinine	78 μmol/l	56.9 μmol/l
ALT	27.94 IU/l	22.9 IU/l
AST	32.36 IU/l	59.2 IU/l
HIV rapid test	Negative	Positive
CD4 count	-	338 cells/mm^3
Cerebrospinal Fluid Analysis		
Cell count (cells/mm^3)	250 cells/μL	1000 cells/μL
Gram stain	Negative	Negative
Glucose	3.5 mmol	-
Xpert ® MTB/RIF	Positive	Positive
Initial treatment	rifampicin, isoniazid, pyrazinamide and ethambutol, prednisolone and chlorpromazine	rifampicin, isoniazid, pyrazinamide and ethambutol, prednisolone and chlorpromazine
Outcome	Complete response	Died after five weeks of treatment

WBC: White Blood Cells; AST: Aspartate Aminotransferase; ALT: Alanine aminotransferase

TREATMENT

With suspicion of bacterial meningitis, the patient was prescribed intravenous ceftriaxone 2g twice daily. Ceftriaxone was stopped after obtaining a chest x-ray and Xpert® MTB/RIF results. Standard anti-tuberculous treatment with rifampicin, isoniazid, pyrazinamide and ethambutol was started and applied for two months followed by rifampicin and isoniazid for seven months. Prednisolone 1.5mg/Kg was initiated simultaneously and was tapered down after two weeks. In addition, for the persistent hiccups the patient was prescribed chlorpromazine 50mg three times daily for the first week and reduced to 50mg twice daily until the hiccups stopped which was after three weeks.

OUTCOME AND FOLLOW-UP

After two weeks of standard anti-tuberculous treatment the patient's condition improved and he was fully conscious and oriented. He was discharged and completed treatment as an outpatient. Hiccups resolved after 3 weeks since starting of treatment.

CASE II PRESENTATION

A 35 years old male patient was admitted to our hospital due to altered mental status for four days prior to admission associated with severe headache, neck pain and hiccups more prominent during the nights reported by his wife. He had a history of unquantified weight loss and severe night sweats. On admission, the patient had a BP of 107/77 mmHg, PR 117 beats/minute, RR 20 breaths/minute, oxygen saturation was 98% and his body temperature was 38.6°C. No focal neurologic signs were present and Kerning and Brudzinski signs were negative. On respiratory examination bilateral bronchial breath sounds localized in all three lung zones and basal crepitations on the right lung were audible. Lymph nodes were enlarged, soft, matted and non-tender at all positions palpated. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Lumbar puncture revealed a slightly turbid CSF with a positive Pandy's test for protein, and a WBC count of 1000 cells/μL with 80% of lymphocytes. Smear microscopy for CSF tested negative for AFB and positive for Xpert® MTB/RIF (negative rifampicin resistance). In addition, CSF tested negative for Gram Stain, VDRL and cryptococcal antigen lateral flow assay (CRAG LFA). The patient tested positive for HIV (rapid test; Alere, Waltham, USA) and his CD4 count was 388 cells/mm3 (4%). Haemoglobin was 10.5 g/dl, WBC 6.7 x 109/L and platelets 380 10^3/μL. ALT was 22.9 IU/l, AST was slightly raised with 59.2 IU/l and serum creatinine was 56.9 μmol/l. The chest X-ray revealed micronodular opacities distributed throughout both lungs (figure 2) and a diagnosis of miliary tuberculosis was reached.

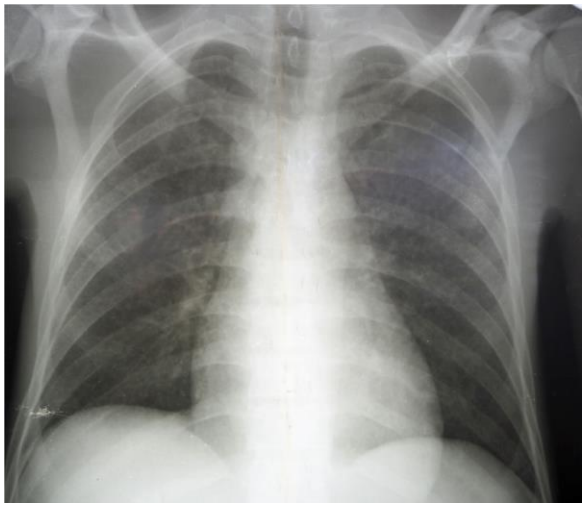

Figure 2: A chest x ray taken on supine position, of the second patient showing uniformly distributed micro nodules involving both lungs

TREATMENT

The patient was started on rifampicin, isoniazid, pyrazinamide and ethambutol, prednisolone 1.5mg/Kg and chlorpromazine 50mg three times daily for hiccups. He was also prescribed I.V. ceftriaxone 2g twice daily, which was stopped after diagnosis of TBM.

OUTCOME AND FOLLOW-UP

After three weeks of treatment in the ward vital signs were stable and the patient was oriented. He was then discharged and continued treatment as an outpatient. After two weeks, we learned from his relatives he developed sudden respiratory distress and died at home.

DISCUSSION

Extra-pulmonary tuberculosis is present in about 20% of HIV-negative and in about 70% of HIV-positive patients with tuberculosis. Among these patients in about 1% the central nervous system is involved (4). Miliary tuberculosis has been reported to be present in 12% of patients with TBM as it has been seen in both our cases (5).

The Xpert® MTB/RIF (Cepheid, Sunnyvale, California, USA) detects *M.tuberculosis* and mutations associated with rifampicin resistance and has revolutionized the diagnosis of respiratory Tuberculosis (TB) with a sensitivity of 93.7% and a specificity of 91.7% in HIV-negative patients (4). In many countries the roll-out of Xpert® MTB/RIF is restricted to respiratory samples, although recently, WHO recommended the use of Xpert® MTB/RIF in extrapulmonary samples (6). In Tanzania Xpert® MTB/RIF is recommended only in patients being able to produce sputum. We acknowledge that it might be difficult to do Xpert® MTB/RIF in other body fluids samples due to limited resources (7). Nevertheless, the long duration of anti-tuberculous treatment, possible side effects, important implications for the timing of start of antiretroviral treatment are arguments for a microbiological confirmation and in our opinion justify this test in cases with high clinical suspicion.

The term hiccups originates from the sound of the event and, it is an uncontrolled myoclonic contraction of the diaphragm. The episode usually takes few minutes, but when it last more than 48 hours it is considered as persistent and when it lasts for than a month it is considered as intractable. The pathophysiology of hiccup is still unknown, but several hypotheses explain the possible mechanism such as stimulation of the N. vagus reflex arch, the phrenic nerves and sympathetic fibres TH6 – TH12 (8). Another explanation might be an irritation of the hiccup centre located in the cervical spine between C3 and C5 (9). There are numerous etiologic factors which have been well described to be associated with hiccups including some neurological and neurosurgical disorders (10). Additionally, hiccups have been associated with infections of the lungs which includes pneumonias and pulmonary TB (9). For our two cases the exact cause remains unclear although we

hypothesize, that the pathology of the upper lung lobe might have caused irritation of the afferent limb of the hiccup reflex arc. In both patients, after starting standard anti-tuberculous treatment and Chlorpromazine the hiccup subsided.

CONCLUSION

Diagnosis of the TBM is challenging. Apart from common symptoms of TBM such as altered mental status, hiccup can be a sign of TB as presented in our two cases. In sub Saharan Africa where the burden of Tuberculosis is very high, Xpert® MTB/RIF in samples other than sputum allows timely diagnosis in patients with a high clinical suspicion.

REFERENCES

1. End_TB_brochure.pdf [Internet]. [cited 2016 Sep 26]. Available from: http://www.who.int/tb/End_TB_ brochure.pdf

2. Thwaites, G.E., Nguyen, D.B., Nguyen, H.D. et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N. Engl. J. Med. 2004;351:1741–51.

3. Marx, G.E., Chan, E.D. Tuberculous meningitis: diagnosis and treatment overview. Tuberc. Res. Treat. 2011;2011:798764.

4. Tortoli, E., Russo, C., Piersimoni, C. et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. Eur. Respir. J. 2012; 40:442–7.

5. Kalita, J., Misra, U.K. and Ranjan, P. Tuberculous meningitis with pulmonary miliary tuberculosis: a clinicoradiological study. Neurol. India. 2004;52:194–6.

6. Microsoft Word - GeneXpert SOP Xpert processing
EPTB specimens_FINAL.doc - GeneXpert_SOP_ Xpert_processing_EPTB_specimens_DRAFT.pdf [Internet]. [cited 2017 Feb 1]. Available from: https:// www.ghdonline.org/uploads/GeneXpert_SOP_ Xpert_processing_EPTB_specimens_DRAFT.pdf

7. Boulware, D.R. Utility of the Xpert MTB/RIF assay for diagnosis of tuberculous meningitis. PLoS Med. 2013;10:e1001537.

8. Noble, E.C. HICCUP *. Can. Med. Assoc. J. 1934 ;31:38–41.

9. Perry, S. and Stevenson, J. An unusual cause of hiccups.
J. Accid. Emerg. Med. 1996;13:361–2.

10. Amirjamshidi, A., Abbassioun, K. and Parsa, K. Hiccup and neurosurgeons: A report of 4 rare dorsal medullary compressive pathologies and review of the literature. Surg Neurol. 2007;67:395–402; discussion 402.