Case Report

Central fever due to hypothalamic lesion in a patient with tuberculous meningitis

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ABSTRACT

Abnormalities of body temperature are perhaps the most common features in many systemic pathologic processes. Such pathologic alterations are nearly always the result of extrinsic factors (for example, systemic pyrogens) which affect the hypothalamic thermoregulatory center by way of circulatory system. Much less common is alterations in temperature regulation resulting from intrinsic lesions of the thermoregulatory center in the hypothalamus. We report a patient with tuberculous meningitis who continued to have persistent fever despite the satisfactory treatment of her tuberculosis. A central thermoregulatory defect was documented and was attributed to a small structural lesion in the anterior hypothalamus.

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Fever is perhaps the oldest and most universally known hallmark of disease.[1] Although the temperature set point mechanism ordinarily maintains body temperature within close limits, the set point can be altered as a result of several systemic pathologic states.[1,2] On rare occasions, abnormalities of temperature regulation result from a local pathologic process involving the central thermoregulatory center in the hypothalamus.[3,7-10] The present paper describes such a case.

Case Report. A 25-year-old lady who was well until 3 weeks prior to admission when she developed fever, malaise, anorexia, increasing headache, nausea, vomiting and blurring of vision. She was otherwise asymptomatic. She gave a history of contact with a patient who had pulmonary tuberculosis. On examination, her temperature was 38^0C, blood pressure = 110/70 mm Hg, pulse = 90/minute and respiratory rate = 22/minute. She was somnolent and ill looking. There was no lymphadenopathy, her chest was clear, and the abdominal examination was normal. She had neck stiffness and a positive Kernig's sign. Brudzinski's sign was negative. Fundoscopic examination showed bilateral papilledema. Apart from slightly exaggerated deep tendon reflexes bilaterally, there were no localizing signs on her neurologic examination. Her investigations revealed: white blood cell (WBC) count of 9,100/mm^3 (with normal differential), erythrocyte sedimentation rate = 42, negative C-reactive protein, serum sodium = 123 mmol/l, serum osmolality = 265 mosm/kg, urine sodium = 78 meg/l and urine osmolality = 180mosm/kg. The renal and hepatic function tests and the serum albumin level were normal. Screening for brucella, malaria and human immunodeficiency virus were negative. Screening of sputum and urine for acid fast bacilli (AFB) was negative. Routine cultures of sputum, urine and blood were unremarkable. Examination of cerebrospinal fluid (CSF) revealed an opening pressure of 280 mm H_2O,

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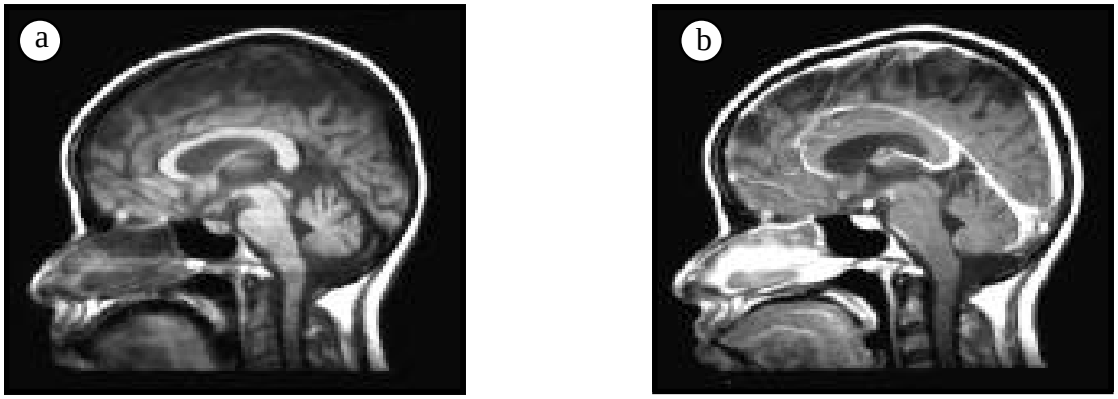

Figure 1 - Magnetic managing resonance of the brain **a)** T1 weighted saggital image before and **b)** after Gadolinium contrast showing an abnormal small enhancing lesion at the anterior hypothalamic region. In addition, there is evidence of meningeal enhancement.

WBC = 343 cells/mm^3 (92% lymphocytes, 5% monocytes and 3% polymorphs), protein = 1245 mg/L and glucose = 2.3 mmol/L (simultaneous blood sugar = 10.8 mmol/L). Gram stain, India ink preparation and routine cultures of CSF were negative. Acid fast bacilli staining and *Mycobacterium* culture were negative. Polymerase chain reaction of *Mycobacterium tuberculosis* in the CSF was positive. A purified protein derivative test was positive (22mm induration). Chest radiograph was normal. Magnetic resonance imaging (MRI) of the brain with and without Gadolinium contrast showed evidence of meningeal enhancement, particularly at the base of the brain consistent with meningitis. The patient was started on 4 anti-tuberculous drugs (Isoniazide 300 mg daily, Rifampicin 600 mg daily, Pyrazinamide 1500 mg daily and Ethambutol 800 mg daily) in addition to Pyridoxine and a course of steroids. She showed remarkable improvement in her clinical status in general and in her meningial irritation symptomatology in particular, over a period of 2 weeks of starting anti-tuberculous therapy. The evidence of improvement was reflected, as well, on a follow-up CSF examination which showed WBC = 178 cells/mm^3, protein = 1157mg/L, glucose = 1.7mmol/L (blood sugar = 5.7mmol/L). Despite the improvement in her clinical condition and CSF profile, she continued to have persistent fever afterward. A detailed screening for sepsis was repeated and failed to disclose any possible etiology for continued fever. An MRI of the brain with and without Gadolinium contrast was repeated then. It showed a small enhancing lesion in the anterior hypothalamus (**Figure 1a & 1b**). The clinical and biochemical endocrine assessment of the hypothalamic – pituitary axis was normal. The interpretation of the persistently elevated temperature was that of a defect in the central thermoregulatory center as a result of the demonstrated hypothalamic lesion, other possibilities having been excluded. The patient was seen in follow-up after one month of discharge from the hospital when she reported that her fever had subsided spontaneously 2 months following anti-tuberculous therapy. A repeat MRI showed some regression in the size of the hypothalamic lesion.

Discussion. In the system of temperature regulation, the integrator and many controlling elements appear to be located in the hypothalamus. Although both anterior and posterior hypothalamic areas are involved in temperature regulation, detectors of temperature, both low and high, are located only in the anterior hypothalamus.[2] Stimulation of the anterior hypothalamus causes cutaneous vasodilation and sweating, and lesions in this region cause hyperthermia, with rectal temperature sometimes reaching 43^{0}C (109.4^{0}F). Posterior hypothalamic stimulation causes shivering, and the body temperature of animals with posterior hypothalamic lesions falls towards that of the environment.[1,2] One of the physiologic alterations in the human core temperature is reflected in the regular circadian fluctuation of 0.5-0.7^{0}C. It is lowest at approximately 6:00 a.m. and highest in the evening. It is lowest during sleep, is slightly higher in the awake but relaxed state, and rises with activity. In women, there is an additional monthly cycle of temperature variation characterized by a rise in basal temperature at the time of ovulation. Temperature regulation is less precise in young children.[1] Although the set point of the human hypothalamic

thermostat maintains body temperature within close limits, it can be altered by pathological states, most notably by the action of circulating pyrogens, which induce fever. Systemic pyrogens, such as interleuken-1, appear to enter the brain at regions in which the blood brain barrier is incomplete (circumventricular organs), and act on the preoptic area of the hypothalamus to induce fever.[1,2,4,9] Abnormalities of temperature regulation may result from a local pathologic process involving the hypothalamus.[3,7-10] In tuberculous meningitis, fever is one of the most prominent clinical features (55-85%).[5] The clinical response to anti-tuberculous therapy is quite variable. Evidence of improvement in CSF profile is reported to be between 2 and 11 weeks.[11] The fact that our patient showed marked improvement in her clinical state, along with the evidence of improvement in her CSF profile as a result of the anti-tuberculous therapy, led us to interpret that the persistence of fever was unlikely related to a systemic process. Rather, it was felt to be the result of the local anterior hypothalamic lesion, that was demonstrated on her cranial MRI. The pathology of the lesion was considered most likely a small tuberculous granuloma. Tuberculomas can be as small as 2 mm in diameter.[6] Abnormalities of temperature regulation due to hypothalamic dysfunction, in patients with tuberculous meningitis, have been observed.[7,8] Dick et al[7] described a patient who developed chronic hypothermia following tuberculous meningitis due to a central defect of thermoregulation. Joshi et al[8] reported 2 patients with tuberculous meningitis and hydrocephalus who developed hypothermia, which was thought to be secondary to pressure on the thermoregulatory center in the posterior hypothalamus. Our patient also displayed transient syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). Mild to moderate hyponatremia is present in roughly 45% of patients with tuberculous meningitis, in some cases constituting a true syndrome of inappropriate secretion of anti diuretic hormone.[5] Secretion of anti-diuretic hormone in our patient was controlled by fluid restriction. The relationship of this syndrome with the central thermoregulatory defect in our patient is uncertain as SIADH is usually associated with posterior hypothalamic dysfunction. Tuberculous meningitis has long been recognized to cause endocrine abnormalities due to dysfunction of the hypothalamic-pituitary axis.[12-14] Our patient did not show clinical or biochemical evidence of endocrine dysfunction. However, such endocrine dysfunction may only become evident months or years after recovery, apparently due to progressive scarring of either the hypothalamus itself or the adjacent basal cisterns.[6]

In conclusion, fever is a common clinical feature of tuberculous meningitis. A delay in the disappearance of the fever after the institution of the appropriate anti-tuberculous therapy is sometimes seen as part of slow response of tuberculous infection in general. However, persistence of fever in our patient despite the evidence of improvement in all other clinical parameters along with CSF profile and the presence of the hypothalamic lesion strongly suggests that the fever was due to a central defect of thermoregulation.

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