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Case Report

Central Diabetes Insipidus as a Manifestation of Congenital Toxoplasmosis. Case Report and Literature Review

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Abstract

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasite with the capacity to infect almost any warm blood animal; it's transmitted to humans in several ways, such as transplacental spread. Most congenitally-infected children are free of symptoms at birth, however among infected newborns 40% have neurological sequelae. Involvement of hypothalamic-pituitary axis is uncommon, when it occurs it usually affects the anterior pituitary and exceptionally the posterior pituitary. In this article we present the case of an infant with congenital toxoplasmosis and central diabetes insipidus, referred to a tertiary care center in Mexico City.

Keywords: *Congenital Toxoplasmosis; Central Nervous System; Hypothalamic-Pituitary Axis; Central Diabetes Insipidus*

Introduction

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasite that has the ability to infect any warm-blooded animal [1]. Toxoplasmosis has a worldwide distribution, and its prevalence varies by geographic locale and socioeconomic strata [2]. In Mexico, seroprevalence ranges from 15 - 50% in the general population [3-5].

Congenital toxoplasmosis (CTox) is a serious manifestation of the disease, resulting from the transplacental passage of *T. gondii* tachyzoites from a primary infected mother to the fetus [6]. The overall rate of CTox in women who seroconvert during gestation has been reported to be between 50% and 60% before the introduction of spiramycin, and 20 to 30% thereafter. Women chronically infected can reactivate the infection during gestation if significantly immunocompromised and also transmit the parasite to their offspring [4].

According to the World Health Organization (WHO) the incidence of CTox changes according to the seropositivity of population - rare in high prevalence countries, common in places with low seroprevalence [1,7]. Generally, seroconversion during gestation is low oscillating between 0.3 and 1.5% depending the country. Worldwide the incidence of maternal primary infection with *T. gondii* is approximately 1 to 8 per 1,000 pregnancies [8].

The risk and severity of the disease depends mainly on the gestational age at transmission. Infection of the fetus at the first trimester may cause severe damages, whereas the fetal disease is less severe in later trimesters [9]. Vertical transmission rates in treated women

are 6% at 13 weeks of gestation, 40% at 26 weeks, and 72% at 36 weeks; clinical signs develop in 61% of the fetuses if infection is acquired at 13 weeks of gestation, 25% if acquired at 26 weeks, and 9% if acquired at 36 weeks. Other factors that can contribute to severity of congenital toxoplasmosis are the virulence of the strain of *T. gondii*, the number of organisms transmitted from the mother to the fetus, the development of immune system, and the number of organs and tissues involved [10].

Although the majority of the children of mothers infected with *T. gondii* are asymptomatic, congenital toxoplasmosis can be devastating and present with multi-systemic conditions [10]. Clinical manifestations include prematurity, jaundice, hepato-splenomegaly, myocarditis, pneumonitis, purpura, chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, epilepsy and mental retardation [11]. Involvement of hypothalamic-pituitary axis is uncommon, when it occurs it usually affects the anterior pituitary and exceptionally the posterior pituitary [9]. We report the case of a patient with congenital toxoplasmosis, who presented with central diabetes insipidus without any other alteration of the hypothalamic-pituitary axis.

Case Report

Newborn male patient from a rural area within Mexico City with a history of being borned by c-section at 32 weeks of gestation due to maternal transvaginal hemorrhage and suspicion of urinary tract infection. The mother deceased in the immediate puerperium due to pulmonary thromboembolism. Apgar scores of 7 and 8, weight 1460g (p15, z-1.05), length 42 cm (p35, z-0.39). During the immediate neonatal period he presented multifactorial jaundice and anemia, for which he received phototherapy for 10 days and blood transfusions. He was discharged from the maternal center after 28 days.

A week after his discharge he was admitted to our tertiary care center due to fever (101ºF), refusal to eat and a brief, resolved, unexplained event (BRUE) characterized by apnea, cyanosis and loss of muscle tone.

Upon his admission he had hypothermia (94.4ºF), bradycardia (80bpm), apnea and was unconscious requiring ventilatory support immediately. Physical exam was unremarkable, he had a weight of 2550 g ($p < 1$, z-5.52), length of 42.5 cm ($p < 1$, z-7.67) and a head circumference of 34 cm ($p < 1$, z-4.11), no skin lesions were seen, he had no hepatosplenomegaly.

Late neonatal sepsis with CNS involvement was suspected. Complete blood count (CBC) reported hemoglobin 12.4 g /dL, leukocytes 8.6 thousand/mcL, neutrophils 23%, lymphocytes 46%, eosinophils 26%, platelets 267 thousand/mcL. *Klebsiella pneumonia* ESBL was initially isolated in a blood culture, for which antibiotic coverage was given with vancomycin and meropenem. Cerebrospinal fluid (CSF) was xanthochromic and showed glucose of 37.1 mg/dL, proteins 534 mg /dL, cells 16 mm^3 of which 39% were segmented, 6% eosinophils, 48% lymphocytes and 7% monocytes. Uranalysis reported a positive leucocyte esterase, negative nitrate and uncountable leucocytes. Liver function tests were within normal limits (ALT 31 U/L); he had a creatinine of 0.19 mg /dL, urea 19 mg /dL and BUN 8.9 mg /dL.

Intraventricular hemorrhage, hydrocephalus and multiple intracranial and paraventricular calcifications were diagnosed by transfontanelar USG and computed axial tomography, no injury to the supraoptic or paraventricular tracts was observed (Figure 1 and 2). Left eye fundus showed a hyperpigmented scar in the upper temporal arch.

Due to the mentioned clinical data, TORCH was suspected, serological tests for cytomegalovirus (CMV) and toxoplasmosis were requested. The patient had Western Blot IgG and IgM positivity for *T. gondii*, treatment with trimethoprim/sulfamethoxazole (10 mg/kg/day every 12 hours) and pyrimethamine (1 mg/kg every 12 hours for 2 days; followed by 1 mg/kg once per day) was started.

Since his admission and practically during his entire hospital stay, the patient presented hydroelectrolytic alterations characterized by hypernatremia (serum sodium up to 161 mEq /L) with elevated serum osmolality (> 300 mOsm /kg H_2O), as well as polyuria (uresis > 5

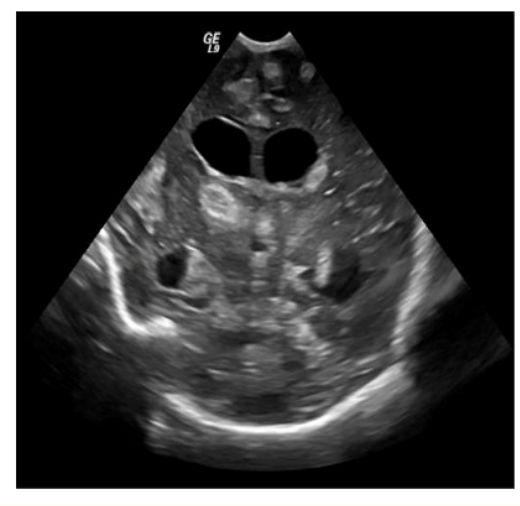

Figure 1

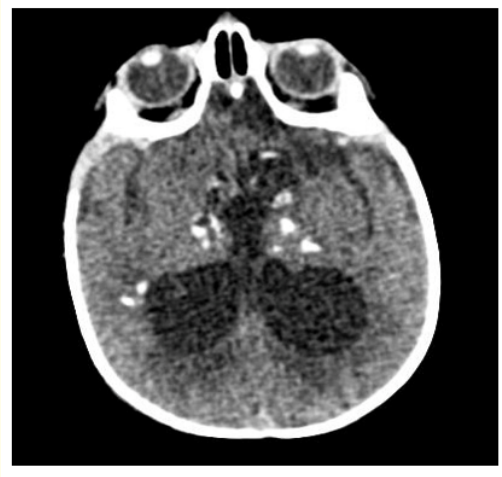

Figure 2

ml /kg /hour) and hyposthenuria (urinary osmolarity < 300 mOsm /kg H_2O, urinary densities <1,005). Initially, this disturbances were managed with enteral water supply. After persisting with the aforementioned disorders, and due to the impossibility of doing a water restriction test, it was decided to give a diagnostic-therapeutic test with subcutaneous desmopressin, obtaining a response and confirming the diagnosis of diabetes insipidus. Subsequent management was performed with desmopressin sublingually at dose response. The rest of the hypothalamic-pituitary axis was assessed without finding any alterations (Table 1); the evaluation of the somatotropic and adrenocorticotropic axis were not reliable due to the malnutrition of the patient and the use of steroids.

Axis	Hormones	
Thyroid	TSH 3.79 uUI/mL	T4L 1 ng/dL
Sexual	FSH 2.6 mUI/mL	LH 1.4 mUI/mL
Prolactin	Prolactin 35.1	

Table 1

The patient's clinical evolution worsened, he presented seizures and multiple apneas After 56 days of hospital stay, he died of acute respiratory distress syndrome secondary to pneumonia associated with health care.

Discussion

CTox is characterized by meningoencephalitis with intense perivascular inflammation that mainly involves the basal ganglia and the periventricular regions [12]. It is probable that one or more hypothalamic centers are involved in this process and, consequently, that alterations in the hypothalamic-pituitary axis become present. However, neuroendocrine disorders in these patients are rarely studied [13].

There are some case reports that document predominantly adenohypophysis dysfunction (growth hormone deficiency, adrenal insufficiency, central hypothyroidism, and hypogonadotropic hypogonadism) [13-17] but very few have reported neurohypophysis involvement. Antidiuretic hormone (ADH) deficiency in an isolated and selective manner as observed in our patient is very rare. Mohamed., *et al*. reported the case of a girl with a history of 2 episodes of neonatal sepsis at 3 and 6 weeks of age, who then started with polyuria, hydroelectrolytic disturbances and neurological disorders that ultimately led to the diagnosis of CTox and central diabetes insipidus [9]. Karadag., *et al*. described a neonate with congenital toxoplasmosis and hydrocephalus who developed diabetes insipidus at 10 days of age [18]. Similarly, Oygür., *et al*. presented a 33-day-old boy who had polyuria, hypernatremia and dehydration secondary to central diabetes insipidus caused by CTox [19].

Central diabetes insipidus in the neonatal period has a high mortality and serious comorbidities [20]. Its diagnosis can be complicated due to the difficulty in quantifying urine, perception of thirst and immaturity in the mechanisms for concentrating urine, among others. Our patient also presented prematurity, sepsis with encephalitis, making the interpretation of the hydro-electrolyte abnormalities even more complicated. Although the dehydration test is capable of guiding the diagnosis, in pediatric patients it should be performed under close supervision because it can result in intracranial hemorrhage, seizures and coma due to severe dehydration and hypernatremia. This test should not be performed on infants.

The quantification of circulating ADH is not useful due to its instability and complexity of analysis. ADH comes from pre-provasopressin, a prohormone that is secreted in conjunction with copeptin (C-terminal fraction). The latter is stable *in vitro* and is easily measured. In adults, copeptin has a good sensitivity and specificity for the diagnosis of diabetes insipidus; but in pediatric patients it has only been shown as a marker of fetal and neonatal stress [21].

Treatment of diabetes insipidus is usually done with oral or intranasal desmopressin [22]. However, these routes may not be safe in neonates with other neurological disorders or in a critical state. The route of administration and dose of desmopressin should always be individualized and tends to vary over time. Pontine myelinolysis is a dangerous complication that can result from abrupt changes in osmolarity caused by the excessive use of desmopressin. When intranasal desmopressin is used, any blockage in the nasal cavity can cause severe hypernatremic dehydration. Swallowing and sedation disorders can impair the absorption of oral desmopressin [20].

It has been described that the subcutaneous administration of desmopressin (vasopressin) can be particularly useful in neonates and individuals with neurological disorders, and that it has a time of action and duration similar to nasal desmopressin [23]. Although this

route was initially preferred, in our patient oral desmopressin tablets were divided and administered sublingually, obtaining a good response with no significant osmotic changes.

Conclusion

The diagnosis and management of this patient was complicated due to his multiple risk factors, which ultimately led to his death. Despite the fact that central diabetes insipidus is an unusual manifestation of CTox, this case and our review of the literature demonstrate that congenital *T. gondii* infection can be a cause of hypothalamic-pituitary disorders.

Diagnosis of diabetes insipidus in neonates and infants requires a high index of suspicion. Persistent hypernatremia despite an adequate supply of fluid, accompanied by hyposthenuria and dehydration are red flags that must be taken into account.

The treatment of diabetes insipidus must be individualized. The use of oral desmopressin administered sublingually may pose a useful tool for the management of this in infants with neurological disorders.

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