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ARE CHILDREN WITH CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS AT RISK OF DEVELOPING HYPOPITUITARISM?

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ABSTRACT

BACKGROUND: Childhood hypopituitarism is a rare clinical syndrome characterized by a deficiency of one or more pituitary hormones. This may result from disorders involving the hypothalamic-pituitary region or the surrounding structures with a diversity of causes.

DESIGN AND SETTING: A retrospective hospital-based study conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia during the period (January 1990 to December 2017).

METHODS: Medical records of patients who developed hypopituitarism secondary to infectious causes were reviewed. Detailed history, clinical manifestations and results of laboratory and radiological investigation were obtained.

RESULTS: During the period under review (January 1990 - December 2017), a total of 247 patients were diagnosed with variable central nervous system (CNS) infections. Only three resulted in variable pattern of hypothalamic pituitary dysfunctions, two with diabetes insipidus (DI) and one with DI and panhypopituitarism. They were at young age 1,6 and 8 months old.

CONCLUSION: Hypothalamic-pituitary dysfunctions, though very rare, may develop in patienst with central nervous system infection. Further prospective studies should be performed to determine the role of CNS infections in the etiology of hypopituitarism.

KEYWORDS : central, nervous system, infections, hypopituitarism, diabetes insipidus (DI)

INTRODUCTION

Childhood hypothalamic-pituitary dysfunction is a rare clinical syndrome characterized by a deficiency of one or more of pituitary hormones. This may result from disorders involving the hypothalamic-pituitary region or surrounding structures. A diversity of causes was reported including craniopharyngioma,post-operation and post radiotherapy, stroke, vascular condition, head injury and autoimmune disease such as hypophysitis. (1-2) Al-Jurrayyan, et al. (3) reported recently in a pediatric age group that congenital causes were more frequent than acquired hypothalamic-pituitary dysfunction.

Infections of the central nervous system (CNS) are increasingly being recognized as a significant cause of hypothalamic-pituitary dysfunction. Although tuberculosis is the most common agent involved, non-mycobacterial agents like viruses, such as cytomegalovirus (CMV), bacteria with Haemophilus influenza, and streptococcal pneumonia, fungal such a candida infection, and protozoa are important causes. There are, however, few reports of other infectious agents as a cause of the hypothalamic-pituitary dysfunction. (1-2,4)

This reports on our clinical experience with hypothalamic-pituitary dysfunctions in patients who survived central nervous system infections in the last three decades (January 1990-December 2017) at King Khalid university hospital (KKUH). KKUH was established in 1982 as the mean teaching hospital of the King Saud University. It provides primary, secondary, and tertiary health care services to the local population and receives referrals from other parts of the country.

Materials and methods:

Medical files of all children with the diagnosis of central nervous system infections, who were admitted to the pediatric service of King Khalid university hospital (KKUH), Riyadh, Saudi Arabia, during the period January 1990 and December 2017, were retrospectively reviewed. (4)

KKUH is one of the major referral hospitals in Riyadh province of the central region of Saudi Arabia and has pediatric intensive care unit and wards of 100 bed capacity with the average admissions of 2000 per year.

Data extraction Includes age, sex, clinical manifestation, and results of all the ancillary laboratory investigation and radiological procedures performed. Details of the hospital course as well as the outcome of illness were also extracted. (5)

RESULTS:

During the period under review (January 1990 - December 2017), a total of 247 patients were diagnosed to have variable central nervous system infections. There mean age was 1.8 years (range 0-14) y. Only three patients were complicated with various hypothalamic-pituitary dysfunction, table 1. They were at a younger age 1, 6 and 8 months. A six months old girl with streptococcal pneumonia developed isolated diabetes insipidus (DI), as well as, a one-month-old girl with congenital toxoplasmosis. An eight-month-old boy suffered from panhypopituitarism with DI. He had virulent streptococcus pneumonia resulted in severe neurological sequelae (figure 1). Two hundred and six were diagnosed with variable hypothalamic-pituitary dysfunction in the same period, with a mean age of 6.8 years (range 0-18).

DISCUSSION:

Hypothalamic-pituitary dysfunction in children is a rare clinical disorder estimated to be 4.21-45.5 cases per 100,000 population. It may present at birth (congenital) or may be acquired. Early diagnosis and treatment promote the best possible outcome. Children with congenital hypothalamus pituitary dysfunction may present with life-threatening hypoglycemia, shock or cholestatic jaundice. Causes of congenital forms may include sept-optic dysplasia, other midline defects syndromes, and mutations of transcription factors involved in the pituitary gland development.

While children with the acquired form typically presented with growth failure and may have other symptoms depending on the etiology and the extent of pituitary hormones deficiency. Acquired forms may result from brain tumors, such as craniopharyngioma, radiation, trauma, infiltration, such as histiocytosis, hydrocephalus, vascular anomalies, and infections. Magnetic resonance imaging (MRI) of the brain is critical for the diagnosis.(1-3,6,7)

Infectious disease of the central nervous system (CNS) may cause hypothalamic-pituitary dysfunction, although, this has not been reported very often and not yet been studied systematically. The most common infectious agent affecting the hypothalamic-pituitary axis is Mycobacterium tuberculosis. (8) Two of our patients have diabetes insipidus (DI), and one male has in addition to DI, panhypopituitarism. He had severed streptococcal meningitis complicated with subdural empyema and hydrocephalus (figure 1).

In most previous case reports, isolated posterior pituitary insufficiency has been described.The infectious agents were group B streptococcus, Haemophilus influenza, and Streptococcus pneumonia. Congenital

cytomegalovirus and Coxsackie B virus were important causes. (9-12) This is in contrast to Schaefer et al. who found no evidence of posterior pituitary insufficiency. (13)

Anterior pituitary insufficiency has been reported following infectious diseases of the central nervous system (CNS) of different etiologies. Schaefer et al. reported four patients with isolated corticotropic hormone insufficiency. In almost all cases, the deficiency was caused by viruses and only one patient caused by meningoencephalitis. (13)

Similar to Al Issa et al.(14) who reported on an infant with diabetes insipidus and panhypopituitarism caused by streptococcal meningitis complicated with subdural empyema and hydrocephalus.This is similar to others reports (15,16), Levy-Shraga et al (17) have shown that pituitary dysfunction with overt clinical symptoms is not frequent consequences of acute meningitis in children and invasive assessment should be reserved for selected cases where there is a clinical suspicion of hypothalamic pituitary impairment.

It is reasonable to assume that the pattern of hormonal insufficiency after an acute infectious process may vary with the type of causative agents, the localization of the brain lesion, as well as with the severity of the disease. Giavoli et al. (18) showed that hypothalamic-pituitary dysfunction following infectious encephalopathy is less frequent in children than in adult, and suggest that the pituitary gland of children may be less susceptible to damage.

Furthermore, Tsiakalos et al. (19) reported in a prospective study where sixteen patients wereinvestigated for pituitary function during the acute phase of infectious meningitis, and 12 months later he concluded that pituitary deficiency which could present at the acute phase or a later stage could develop in considerable proportions of patients with acute infectious meningitis.

In conclusion children with the central nervous system (CNS) infections of various etiology are at risk of developing hypothalamic-pituitary dysfunctions, although. Low, but could be life-threatening. The pediatricians should be aware of these prospective studies should be conducted to evaluate the hypothalamic-pituitary axis during the acute phase of the infection, and a few months later, as symptoms are non-specific.

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare

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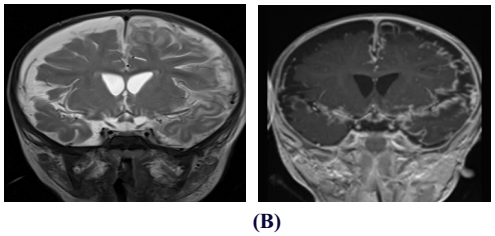
Figure 1: Coronal T2 (A) and coronal T1 post contrast (B) weighted magnetic resonance images of the brain showing mildly dialted lateral ventricles (arrow) and subdural empyma with diffuse leptomeningeal enhancement (arrowhead) in an 8 month old boy.



(A) **(B)**

Table 1, Demographic data of patients with hypothalamic-pituitary dysfunction

Patient	Age	sex	Clinical manifestations	Infectious agent	Endocrine dysfunction
1	6 m	F	Fever, lethargy	S.pneumonia	DI
2	1 m	F	Fever, seizure	Toxoplasma	DI
3	8 m	M	Fever, irritable	S.pneumonia	DI,panhypopitutrism

M-male,F-femal,m-months
S.pneumonia-Streptococcus. pneumonia
Diabetes insipidus (DI), Panhypopit- Panhypopituitarism

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