Growth Impairment in Acute Central Infectious Diseases

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J Pediatr Infect Dis 2019;14:11–12.

Abstract

Acute meningitis is an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that still causes morbidity and mortality. Among the sequelae of meningitis, endocrine complications have been reported in patients recovering from acute central infectious diseases. Although the results of the studies are conflicting, the most common pituitary hormone deficiency during the acute phase or at 1-year follow-up evaluation is growth hormone deficiency, which results in growth impairment in children and a dysregulation of body composition and lipid metabolism throughout life. The mechanisms involved in growth failure secondary to meningitis are unknown. Therefore, endocrinological evaluation, including clinical, auxological, and hormonal assessments, should be performed during the acute phase of the infection and during recovery.

Keywords
- growth
- hypopituitarism
- central infectious diseases

Introduction

Acute meningitis is an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that still causes morbidity and mortality.[1] Among the sequelae of meningitis, endocrine complications have been reported in patients recovering from acute central infectious diseases. Children affected by tubercular meningitis (TBM) may experience significant growth impairment, despite prompt therapeutic intervention. The mechanisms involved in growth failure secondary to TBM are unknown. Both cerebral edema and inflammation have been implicated in the pathogenesis.[2] Some studies reported that TBM may cause hypothalamic–pituitary alteration in affected patients, with growth hormone (GH) release impairment.[3,4] Indeed, in a previous study conducted in children several years after recovery from tuberculous meningitis, GH deficiency (GHD) was observed in 20% of the patients.[4] However, as for bacterial and viral meningitis, the results are conflicting. Some studies found no pituitary dysfunction following viral and bacterial meningitis and suggested clinical growth monitoring as the sole follow-up measure and do not advice laboratory examination, except for selected cases.[5–7] On the contrary, other studies documented that meningitis may affect the hypothalamus and the pituitary, causing a deficient hormone secretion.[8–10] The most common pituitary hormone deficiency during the acute phase or at 1-year follow-up evaluation is GHD.[10,11] In a retrospective study on patients with acute bacterial and viral meningitis, 28.6% had isolated GHD.[11] Furthermore, a prospective study underlined the risk of hypopituitarism both during the acute phase and at follow-up. In particular, the risk of GHD seems to be high in the acute phase, 6 and 12 months after the meningitis episode. In this regard, the authors demonstrated a GHD in 18.7% of patients.[8]

received
December 22, 2016
accepted after revision
November 5, 2017
published online
December 29, 2017

Issue Theme Central Nervous System Infections; Guest Editor, Elena Bozzola, MD

DOI https://doi.org/10.1055/s-0037-1615785.
ISSN 1305-7707.

Some authors demonstrated that 6 months is a too short follow-up in meningitis to exclude a pituitary dysfunction, suggesting the importance of a longer control period.[9] These studies indicate the need of endocrine evaluation and pituitary function testing, to reveal the risk of GHD.[8,10] In literature, the incidence of hypothalamic–pituitary dysfunction following infectious diseases of the central nervous system (CNS) may have been underestimated. Some authors affirm that hypopituitarism usually relates to the severity of the disease, type of causative agent, and site of the infection.[12] Postmeningitis GHD has been described and confirmed by provocative tests in adults.[8,10]

Other authors suggested a possible role of autoimmunity in the pathogenesis of hypopituitarism in patients recovering from meningitis. In fact, antipituitary and antihypothalamus antibodies have been found during the acute phase of meningitis and at 1-year follow-up in 35 to 50% of the patients. However, no correlation was detected between pituitary dysfunction and the presence of antibodies at any time during the follow-up period.[11] We, therefore, may speculate that acute meningitis triggers an autoimmune process, which may lead to hypopituitarism.

Most of the patients deceased for acute bacterial meningitis had varying degrees of axonal injury, ranging from mild to very severe, at autoptic examination (Gerber I). Consequently, we may hypothesize that hypothalamic–pituitary insufficiency may result in axonal injury.

Insulin-like growth factor-I (IGF-I) and its binding protein IGF-binding protein-3 (IGFBP-3) are the most important peripheral mediators of GH actions. Furthermore, circulating levels of IGF-I and IGFBP-3 are considered to be suggestive for a diagnosis of GHD, with a sensitivity and specificity of 70 and 95%, respectively.[13]

In a study conducted on adult patients with previous acute central infectious diseases, IGF-I concentration was low, notwithstanding normal GH peak after GH stimulation test. Therefore, no patient was diagnosed with GHD.[8] In children recovering from meningitis, GH increased after stimulation test but the parameters showing the activity of GH, IGF-I, and IGFBP-3 were found to be low, compatible with a neurosecretory dysfunction of GH.[7]

In childhood, since hormones regulate growth and pubertal development, the implications of hypopituitarism may affect physiological development. Moreover, GH/IGF-I axis plays an important role in the regulation of body composition and lipid metabolism throughout life. Therefore, endocrinological evaluation, including clinical, auxological, and hormonal assessments, should be performed during the acute phase of the infection and during recovery.

We propose at first the evaluation of growth in children. Anthropometric measurements should be performed by a professional nurse and reported in the clinical diary, according to the World Health Organization (WHO) standards. Stature should be measured in patients when barefoot with a stadiometer. It should be compared with age references and expressed as standard deviation score (SDS). Moreover, height SDS should be related to midparental height. A longitudinal analysis of growth should be conducted at interval periods and expressed as height velocity.

After the auxological evaluation, a biochemical assessment of GH–IGF–I axis may be suggested. The most commonly used screening tests to evaluate GHD are IGF-I levels and GH stimulation tests. IGF-I has limited sensitivity due to a possible overlap with normal values.[14] In fact, low levels of IGF-I may be not associated with GHD, but with low energy intake and, less commonly, GH receptor and postreceptor defects.[15,16]

Stimulation tests are indicated to confirm the diagnosis of GHD in childhood for selected cases showing a reduced growth velocity or in the hypothesis of other clinical causes of hypopituitarism.

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