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Full Length Research Paper

Linear growth in children after acute meningitis: A controlled study

Wail Said Seleem[1], Ashraf Soliman[1]* and Ahmed Elawwa[1,2]

[1]Department of Pediatrics, Hamad General Hospital, P. O. Box 3050, Doha, Qatar.
[2]Alexandria University, Alexandria, Egypt.

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In this study, we recorded and analyzed the growth data of 40 children with acute meningitis (age 5.8 ± 3.1 years) for a year or more after treatment, and compared them with their age and sex matched healthy siblings (n = 100). None of the patients had any meningitis complications that could affect linear growth. None of them were underweight and/or stunted for one year or more after treatment. The height standard deviation scores (HtSDS) of patients decreased significantly from -0.06 ± 0.95 at the onset of meningitis to -0.46 ± 1 after a year or more of follow-up and were significantly lower than those for their normal siblings (controls) (0.31 ± 0.5). Fifteen out of the 40 patients had decreased HtSDS > -0.5, while 3 had decreased HtSDS > -1 after > 1 year of follow-up. The body mass index (BMI) of patients significantly increased after 1 year or more of the acute attack, but did not differ from the BMI for the controls. One patient and none of the controls had BMISDS > 2 at presentation. Furthermore, 5/40 patients and 2/100 children from the control group had BMISDS > 2 after 1 year or more of follow-up. The HtSDS decreased and BMI increased significantly in both groups with septic (n = 10) and aseptic meningitis (n = 30) with no significant difference among the 2 groups. It was concluded that long term growth delay and overweight and/or obesity appear to be risk factors following an acute attack of both septic and aseptic meningitis.

Key words: Meningitis, pituitary dysfunction, body mass index, growth.

INTRODUCTION

Severe infectious diseases that occur during periods of rapid growth may also affect growth and nutritional status of children in both developing and developed countries (Scrimshaw et al., 1968; Mata et al., 1972; Santosham et al., 1979). Acute bacterial meningitis continues to be an important cause of mortality and morbidity in neonates and children throughout the world, affecting mainly infants younger than one year and children 5 to 10 years of age (Kwang, 2010). Meningitis that occurs at an age when brain growth is still in progress may result in permanently debilitating neurological sequelae. During this illness, the host response to infection and the reduction in food intake may contribute to nutritional deficiencies (Eiivlou et al., l989).

Infections of the central nervous system (CNS) have been occasionally associated with pituitary insufficiency in retrospective studies and case reports. In one retrospective study of 49 young patients with tuberculous meningitis, hypopituitarism was documented in 20% of them (Lam et al., 1993). Growth hormone (GH) and gonadotropin deficiencies were the most common abnormalities observed. In two retrospective studies published in 2008, partial hypopituitarism after CNS infections was found in 20 and 28% of patients, respectively (Tanriverdi et al., 2008; Schaefer et al., 2008). Isolated severe GH deficit was found in the second study (Schaefer et al., 2008). In a prospective study in 16 patients with acute bacterial, cryptococcal or viral meningitis, it was disclosed that in the acute phase of meningitis, 37% of patients had pituitary hormone deficiencies. After 12 months, 31% of

*Corresponding author. E-mail: atsoliman@yahoo.com.

these patients had at least one anterior pituitary hormone deficiency (GH and /or ACTH) (Tsiakalos et al., 2010). These data suggest that CNS infections should be included in the differential diagnosis of hypothalamic-pituitary deficiency and that patients with previous meningitis are at increased risk of hypothalamic-pituitary dysfunction.

Hypothalamic pituitary infections may occur secondary to adjacent bacterial meningitis, and it has been reported in pneumococcal, streptococcal, listerial, and tuberculous meningitis (Lam et al., 1993; Tuazon and Migulues, 2001). Shock resulting from infection (meningitis) can result in pituitary vascular insufficiency and acute necrosis (Tuazon and Migulues, 2001). The onset of hypothalamic-pituitary hormone deficiency may be difficult to diagnose during acute meningitis and its deleterious effect on linear growth may take few months to be clinically detected (Tuazon and Migulues, 2001). To the best of our knowledge, no previous prospective controlled study has followed linear growth in children for a year or more, following acute meningitis. The study was, therefore, aimed at investigating the impact of meningitis (septic and aseptic) on linear growth and body mass index (BMI) by examining the long-term effects in otherwise healthy children.

PATIENTS AND METHODS

All the children with meningitis who were seen primarily at our institution from 2006 to 2007 were studied. This study was approved by the ethical committee of Hamad Medical Center, and informed consent was obtained from all parents of the children included in the study. Forty children with acute meningitis were admitted to Hamad General Hospital, Department of Pediatrics, Doha, Qatar. This number consisted of 18 girls and 22 boys, with age ranging between 1.5 and 5.2 years (average; 3.2 ± 1.1 years). Septic meningitis was diagnosed by clinical symptoms and/or signs of meningitis with an accompanying cerebrospinal fluid (CSF) pleocytosis and identification of the causative microorganisms. Ten children with septic meningitis were identified. CSF culture showed *Streptococcus pneumonia* in 5, *Neisseria meningitidis* in 3 and *Haemophilus influenza* in 2 patients. The other 30 patients were diagnosed with aseptic meningitis (symptoms and/or signs of meningitis and CSF pleocytosis with no identification of specific micro-organism in the blood and CSF cultures). None of the patients had any sequelae that could affect growth (paresis, spasticity, ataxia or mental affection) Children with syndromes, malnutrition, anemia, chronic or systemic disease, and/or those with skeletal abnormalities were excluded. In total, 100 normal age- and sex-matched healthy siblings of the patients were randomly selected to serve as controls for anthropometric data. This was to serve as control for environmental and social factors.

Two expert dietitians did not find any significant difference in the quality or quantity of food intake of patients versus their siblings (controls) using the multiple pass recall (MPR) method for 48 h. This dietary recall is a retrospective method of dietary assessment where the parent of the child is interviewed about their food and beverage consumption during a defined period of time, typically the previous 2 days. The MPR method is a staged approach to the dietary recall. It follows the pattern of a free and uninterrupted recall of intake, followed by detailed and probing questions about intake (including quantities consumed) and concluding with a review of everything that was previously recalled, allowing for the addition of any items not remembered up to this point, and often also the location of the consumption.

Patients did not differ from the healthy controls in age, gender, or race, body mass index (BMI) or HtSDS. Anthropometric measurements including length or height was measured during hospitalization and after 1 year or more after hospitalization. For children aged < 2 years, supine length was measured using a standard-length measuring board. Height for children aged > 2 years was measured with a stadiometer. Weight during hospitalization and the follow-up period was determined on the standard hospital infant or upright scales. These scales were checked annually for their accuracy. Height and weight measurements were evaluated using the Centre for Disease Control (CDC) growth standards (Kuczmarski et al., 2000). The height standard deviation score (HtSDS) and BMI were calculated and compared to those for controls.

RESULTS

At the time of hospital admission, only one child was comatose, four suffered from hypothermia (temperature < 36.6°C), 1 was in shock (blood pressure < 60 Torr systolic), and 8 were dehydrated (with serum sodium > 135 mmol/L and urine specific gravity > 1.03). One patient had the syndrome of inappropriate diuretic hormone (SIADH) (defined as a serum Na concentration < 125 mmol/L and urine specific gravity > 1 .022). In addition, 32 children were febrile (> 38.0 c). Clinical manifestations at diagnosis are summarized in Table 1. None of the children included in this study developed other significant diseases or neurological sequel involving cognitive and motor function, during the period of follow-up.

Furthermore, on admission, the HtSDS and BMI of all patients did not differ from those for normal children. The growth data of the 40 children with acute meningitis (Table 2) were compared with normal age-matched siblings for two years. None of the patients developed underweight and/or presented with stunting for one year or more after treatment. The HtSDS of patients decreased significantly after a year of the acute meningitis and were significantly lower than those for normal controls. Moreover, 15 out of the 40 patients (37.5%) had decreased HtSDS > -0.5, while 3 (7.5%) had decreased HtSDS > -1 after > 1 year of follow-up. The BMI of patients significantly increased after 1 year or more of the acute attack, but did not differ from the BMI for the controls. One patient and none of the controls had BMISDS > 2 at presentation. Five out of the 40 patients and one child from the control group had BMISDS > 2 after 1 year or more of follow-up. Dietary evaluation of food intake of patients versus their siblings (controls), using the recall method for 48 h, did not show significant difference between the 2 groups.

Comparison of growth data of children with septic versus aseptic meningitis (Table 3) showed that in both groups, after 1 year or more of acute meningitis, there

Table 1. Clinical manifestations of patients with meningitis (n = 40) at presentation.

Symptom/sign at presentation	Percentage (%)
Fever	80
Lethargy	80
Vomiting	75
Respiratory infection	50
Runny nose	50
Seizure	10
Diarrhea	17.5
Otitis media	12.5
Pleocytosis	100
Increased CSF protein	100
Decreased CSF glucose	62.5

Table 2. Growth data of patients with meningitis (n = 40) versus controls.

Data	Growth data before presentation	At presentation	After > 1 year	Controls	After > 1 year
Number	40	40	40	100	100
Age (year)	1.3 ± 2.9	5.8 ± 3.1	6.9 ± 3*	5.5 ± 2.1	6.8 ± 2.6*
L/HtSDS	0.15 ± 0.7	(-) 0.06 ± 0.95	(-) 0.46 ± 1*#	0.12 ± 0.4	0.31 ± 0.5
BMI	14.9 ± 2.3	15.7 ± 2.3	16.7 ± 2.73*	16.2 ± 1.9	16.8 ± 2.1

L/HtSDS, Length / height standard deviation scores; BMI, body mass index.*p < 0.05 after vs. at presentation; # p < 0.05 patients vs. controls.

Table 3. Growth data of patients with aseptic versus septic meningitis.

Data	Aseptic		Septic	
	At presentation	After > 1 year	At presentation	After > 1 year
Number	30	30	10	10
Age (y)	5.6 ± 3.3	6.7 ± 3.3*	7.2 ± 1	8.3 ± 1.1*
L/HtSDS	(-) 0.057 ± 1.1	(-) 0.47 ± 1*	0.002 ± 0.7	(-) 0.28 ± 0.7*
BMI	15.8 ± 2.5	16.7 ± 2.9*	15.4 ± 0.8	16.9 ± 0.95*

L/HtSDS, Length / height standard deviation scores; BMI, body mass index. * p < 0.05 after vs. at presentation; # p < 0.05 septic vs. aseptic patients.

was a significant decrease in the HtSDS and increase in the BMI. Also, HtSDS and BMI did not differ between the 2 groups either before or after treatment.

DISCUSSION

The patients with acute septic and aseptic meningitis were uniformly well-nourished at the onset of meningitis. Their HtSDS and BMI were similar to that of normal children in the general population. However, many children in the same patient population developed a significantly decreased HtSDS and increased BMI one year after their episode of acute meningitis. There was a tendency for the children to gain more weight than expected during the follow-up after meningitis. In all, 12.5% of the children were overweight after 1 year or more of follow-up. Both increased appetite and/or concerned parents tending to overfeed their children and decrease their exercise activities after a potentially debilitating serious illness, were proposed as potential mechanisms for this phenomenon. In another study, the long-term follow-up evaluation of children after hospitalization for H influenzae meningitis showed that 43% developed overweight (21/49) (weight for-height > 75th percentile) (Eiivlou et al., l989). Three-day food record of patients after 6 months of acute meningitis showed a statistically significant increase in estimated

calories consumed between the third and sixth month after hospitalization (Eiivlou et al., l989). However, food intake evaluated by the recall method for 48 h did not reveal difference between our patients and their siblings.

Brain cells, including neurons, microglia, endothelial cells and astrocytes can produce interleukin-1-b (IL-1 b) in response to various physiological and pathological stimuli, including meningitis (Monje et al., 2002). IL-1b administration in the CNS has been reported to produce 'stress-like' effects on behavior, food intake, monoamine neurotransmitters, hypothalamic pituitary adrenal axis activity and immune function (Connor et al., 1998; Weiss et al., 1989; Bluthe et al., 1992a, 1991, 1992b, 1996; 1995; Linthorst et al., 1995). Central IL-1 production appears to be an important factor in the regulation of body weight by leptin. Therefore, it is tempting to speculate that CNS cytokines released during meningitis are responsible for pyrexia, corticotropin releasing hormone dysfunction and hypothalamic-pituitary dysfunction, including appetite regulation (Berkenbosch et al., 1987; Sapolsky et al., 1987).

Despite normal or high BMI, linear growth appeared to be adversely affected by acute meningitis. Overall, 15 out of the 40 patients had decreased HtSDS > -0.5, while 3 had decreased HtSDS > -1 after > 1 year of follow-up. This finding excluded under-nutrition as a cause of this slow growth. Bacterial meningitis is a foremost infectious cause of neuronal degeneration of the hippocampus. Clinically, neuronal damage is responsible for permanent neuro-psychological disability in a large fraction of survivors. Not only are neurons killed during experimental meningitis, but neurogenesis is also negatively affected by intracranial inflammation and cannot compensate for neuronal damage. The net result of experimental meningitis is a net decrease of newly formed neurons early and at 3 weeks after induction of the inflammatory process, through a combination of decreased proliferation and altered differentiation (Olaf et al., 2007; Johann and Stephen, 2006). This process can involve the hypothalamic-pituitary area. Recently, isolated or combined pituitary deficiencies, has been shown to develop in a considerable proportion of patients following acute infectious meningitis. These deficiencies may be either transient or permanent, and may occur immediately or few months later. The frequency of this long term anterior pituitary dysfunction after acute meningitis may be more common than hitherto reported (Lam et al., 1993; Tanriverdi et al., 2008; Schaefer et al., 2008; Tsiakalos et al., 2010; Tuazon and Migulues, 2001). These data suggest that decreased linear growth may be explained by decreased growth hormone (GH) secretions and consequently insulin-like growth factor-I (IGF-I) production.

The fact that the children with meningitis in this study seemed to be completely "normal" with regards to height and weight may not be representative of children with meningitis in other regions of the world. However, this population may offer opportunities for particular clinical observations in comparison with similar population(s). In conclusion, long term growth delay and overweight and/or obesity appear to be risk factors following an acute attack of both septic and aseptic meningitis.

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