Eur. J. Oncol., vol. 14, n. 1, pp. 53-56, 2009

Diencephalic syndrome and brain tumours: a rare cause of growth failure

Sindrome diencefalica e tumori cerebrali: una rara causa di deficit di crescita

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Summary

Diencephalic syndrome (DS) is a relative rare disease characterized by a complex of signs and symptoms secondary to hypothalamic dysfunction. In most cases, this disease is due to low grade gliomas of the anterior hypothalamus or optic nerve. These tumours associated with DS seem to have a more aggressive behaviour than others astrocytomas located in the anterior hypothalamic region. This syndrome should be considered in the differential diagnosis of children with growth failure. It is a condition commonly observed by primary care physicians and it is extremely important to recognize it because of the severity of the conditions which may be associated with it. Eur. J. Oncol., 14 (1), 53-56, 2009

Key words: **failure to thrive, diencephalic syndrome, hypotalamic gliomas**

Riassunto

La sindrome diencefalica è una malattia relativamente rara caratterizzata da un complesso di segni e sintomi secondari ad una disfunzione ipotalamica. Nella maggior parte dei casi è causata da gliomi di basso grado dell'ipotalamo anteriore o del nervo ottico. Questi tumori associati alla sindrome diencefalica sembrano avere un comportamento più aggressivo rispetto ad altri astrocitomi localizzati nella regione ipotalamica anteriore. Questa sindrome dovrebbe essere considerata nella diagnosi differenziale di bambini con ritardo di crescita. È estremamente importante riconoscerla per la severità delle condizioni che possono essere associate. Eur. J. Oncol., 14 (1), 53-56, 2009

Parole chiave: **deficit di crescita, sindrome diencefalica, gliomi ipotalamici**

Cause of failure to thrive

Failure to thrive (FTT) is a condition defined by poor weight gain and physical growth failure over an extended period of time in the pediatric age. It is related to inadequate intake, deficit of absorption and increased metabolic demand. The causes of FTT can be various (Table 1). In most cases, growth failure occurs because of environmental neglect or emotional deprivation although a possible organic cause should be often considered (1). FTT is commonly observed by primary care physicians.

Received/Pervenuto 14.4.2009 - Accepted/Accettato 28.4.2009
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Table 1 - Causes of failure to thrive

Prenatal causes	• Prematurity with complications • Maternal malnutrition • Toxic exposure in utero • Alcohol, smoking, medications, infections • IUGR (intrauterine growth restriction) • Chromosomal abnormalities
Postnatal causes	**Inadequate intake** • Lack of appetite [eg, iron deficiency anemia, CNS (central nervous system) pathology, psychosocial disorder, chronic illness] • Food not available (eg, type or volume of food not appropriate, feeding technique, parental-infant interaction problems ,withholding of food) • Inability to suck or swallow (eg. CNS or muscular pathology) • Vomiting (eg, metabolic disorders, obstruction, urinary tract infection, increased intracranial pressure,drugs, systemic illness) • Gastroesophageal reflux and esophagitis **Deficit of absorption and/or use of nutrients** • GI (gastro intestinal) disorder (eg, cystic fibrosis, celiac disease, Schwachman-Diamond syndrome, chronic diarrhea) • Renal: renal failure, renal tubular acidosis • Inborn error of metabolism • Chronic infection [eg, HIV (human immunodeficiency virus) tuberculosis, parasites] • Endocrine: hypothyroidism, diabetes *mellitus*, growth hormone deficiency **Increased metabolic demand** • Hyperthyroidism • Chronic disease [eg, heart failure, BPD (borderline personality disorder)] • Chronic inflammatory conditions (eg, inflammatory bowel disease, *lupus erythematosus*) • Renal failure • Malignancy • Diencephalic syndrome

However, many infants with FTT are not identified unless careful attention is paid to plotting growth parameters or not adequately investigated for organic diseases.

Diencephalic syndrome and brain tumours

Diencephalic syndrome (DS) is a rare disorder of infancy and childhood characterized by profound emaciation and failure to thrive, in spite of apparently normal caloric intake with persistent inability to gain weight or weight loss during the period of growth (2, 3). Regardless of severe emaciation, the linear growth is maintained. This syndrome is also mainly characterized by the absence of cutaneous adipose tissue, hyperactivity, irritability, euphoria, alert appearance and autonomic disturbances (Table 2) (4, 5).

It classically occours in association with low grade glioma of the anterior hypothalamic or chiasmatic region (6, 7). In spite of low-grade histological features, these tumours are generally larger at presentation, they occour at an earlier age and tend to have a more aggressive behaviour than other hypothalamic-chiasmatic astrocytomas (8). In smaller percentage (about 6%), other tumours such as craniopharyngioma, ependymoma and germ cell tumour located in the anterior hypothalamus, are also described in association with DS (9).

The presence of the tumour may explain the associated clinical findings including nystagmus, strabismus, optic atrophy and signs and symptoms of increased intracranial pressure (10).

Table 2 - Clinical features of diencephalic syndrome

Clinical features	%
Emaciation	100
Alert appearance	87
Hyperkinesia	72
Vomiting	68
Euphoria	59
Pallor	55
Nystagmus	55
Hydrocephalus	33
Optic atrophy	24
Tremor	23
Sweating	15
Papilledema	<5

The mechanism of the growth failure and endocrinologic findings in DS are still unknown. The specific form of failure to thrive occurs with elevated growth hormone suggesting a model of acquired partial GH (growth hormone) resistance. The dysregulation of GH-related pathways involved in the regulation of metabolism and adiposity might explain the loss of subcutaneous tissue observed in children with DS (11, 12). Therefore, TNFα (tumour necrosis factor α) has been suggested to be a mediator implicated in the cancer-cachexia syndrome (13).

Physicians should take into account DS in the differential diagnosis of children with failure to thrive (14, 15). This syndrome commonly affects children younger than 12 months with a mean symptoms onset age of 6 months (16). The initial presentation is emaciation and diagnosis may be delayed in the absence of any neurologic findings. The absence of gastrointestinal symptoms and the conservation of a normal growth rate should suggest this disorder in an infant with poor weight gain.

In the suspect of DS, a careful ophthalmic examination aiming to discover the visual abnormalities related to tumour and a neuroradiological examination should be performed. Moreover, since the hypothalamic gliomas associated with DS are generally more aggressive, in order to exclude a possible leptomeningeal dissemination, spinal imaging MRI (magnetic resonance imaging) and cerebrospinal fluid analysis are also advocated.

Supplemental feeding not associated to treatment of the tumours does not lead to the syndrome recovery. Without treatment, most of the patients dies within 12 months after the onset of symptoms. A normalization of the weight gain and endocrine function may be obtained only after the treatment of the hypothalamic lesion. The optimal therapy is still object of discussion. Options include surgery, radiation therapy and chemotherapy. Complete surgical removal of the hypothalamic tumour is generally impracticable due to its anatomic location. A biopsy might be performed for the initial evaluation if the diagnosis of the tumour type is doubt, and an emergency derivation may be necessary in presence of hydrocephalus. Although hypothalamic astrocytomas are very radiosensitive, radiotherapy is employed only in selected cases for the high risk of endocrinological and neuropsychological sequelae. Furthermore, radiation therapy may have played a role in malignant transformation (17). Combined chemotherapy with carboplatin and vincristine generally represents the first choice-treatment for children with low grade tumours that are primarily chiasmatic or hypothalamic in their origin (18, 19). However, some studies have showed that in children with DS the prognosis is worse than in children without DS with low grade astrocytomas of the anterior hypothalamic or chiasmatic region similarly treated (20). These findings could suggest a relationship between the aggressive clinical behaviour of the astrocytomas and the onset of symptoms and signs of DS.

Conclusions

Diencephalic syndrome is a relative rare disease but it should be considered in the differential diagnosis of other disorders with growth failure. Early diagnosis, adequate treatment and close follow up may lead to appropriate management of both tumour and growth.

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