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Growth of children with Langerhans cell histiocytosis

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Abstract Diseases in childhood have an impact on growth. The influence of Langerhans cell histiocytosis (LCH) on growth has never been studied well. Recently a patient with LCH was treated with human growth hormone (GH) because of severe GH deficiency due to LCH involvement of both the hypothalamus and pituitary. This led us to review our charts from 1971 onward for evaluation of the growth patterns in patients with LCH. Here the long-term growth of 22 patients with LCH is reported, the median follow up being 7 years and 1 month. The height data were converted into standard deviation scores (SDS). At diagnosis the mean SDS of patients with isolated LCH at diagnosis was 0.04 and –0.37 in patients with disseminated LCH. Of the total group, 12 patients did not show any influence from the LCH or therapy on their growth. The remaining 10 patients reached, after a minimum of 3 years, a percentile clearly higher than that at diagnosis. However all the ten above mentioned patients, either isolated or disseminated LCH, had a lesion in the facial side of the skull.

Conclusion GH deficiency is not a common manifestation of LCH in childhood and GH provocation tests are only indicated when there is a poor or decelerating growth rate. In our patients the number of organs involved and/or the treatment modality did not influence the growth in all but one.

Key words Langerhans cell histiocytosis · Growth · Growth deficiency · Childhood

Abbreviations *GH* growth hormone · *hGH* human growth hormone · *LCH* Langerhans cell histiocytosis

Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, can occur as an isolated or as a disseminated disease. LCH can affect almost every organ and exacerbations and spontaneous remissions can occur. In general, isolated LCH has a benign course, while disseminated LCH is more severe and tends to be progressive [7].

Short stature in LCH is considered to be a well known complication [1, 10]. The incidence of short stature in LCH secondary to growth hormone (GH) deficiency has been estimated to be less than 1% [6].

The course of growth of children is an index for their health. We studied growth patterns of children with LCH. Factors that could influence growth of patients with LCH are: anterior pituitary destruction, diabetes insipidus, catabolic effects of a chronic disease, glucocorticoid therapy, effects of X-ray therapy given to lytic lesions of the skull, spine or orbits [1], or malabsorption due to gastro-intestinal lesions [9]. In our patient population, one patient developed such a severe growth hormone (GH) deficiency that he was treated with human growth hormone (hGH),

extracted from human pituitary gland. This patient is described in greater detail.

Patients and methods

During the last 22 years (February 1971–August 1993), 26 patients with biopsy proven LCH were treated in the Sophia Children's Hospital Rotterdam. Height data were collected from the medical chart of each patient at time of diagnosis, 3-monthly during the 1st year, in the following 2 years twice a year and once every year afterwards. Four patients were not suitable for our study (because of shortage of height data in three patients and in one patient puberty was already started). Recurrence of LCH or onset of the pubertal growth spurt was considered to be a cut-off point.

In order to compare height data of patients who differ in age and/or sex the height data were converted into Standard Deviation Scores (SDS = Z-score). SDS is the difference between the patient's height (X) and the age- and sex- appropriate population mean height (Y) divided by the standard deviation of the population mean (SDS = X-Y/SD).

When a patient is taller than average for comparable age and sex the SDS is positive. (For example, the matching SDS for the 97th percentile is 1.88.). To study the course of the growth every SDS has been subtracted from the SDS at diagnosis. The found value is called the delta SDS. Growth along the percentile results in a delta SDS equal to zero.

If one organ system (bone, lymph nodes or skin) is involved, LCH is considered isolated, in disseminated LCH, two or more organ systems are affected. In our institution patients with disseminated LCH were treated with chemotherapy (a combination of vinblastine, prednisone, mercaptopurine and methotrexate) for a period of 60 weeks. Children with isolated LCH were followed or treated locally. Only in cases of polyostotic LCH or progression of the disease chemotherapy was given.

Case report

After a 2-month history of diabetes insipidus, a 3-year-old boy was admitted to the Sophia Children's Hospital of Rotterdam because of complaints of fainting and progression of his disease. X-ray of the skull showed two clear osteolytic lesions, left parietal and dorsal, which after biopsy proved to be LCH. Lesions were also seen in the soft tissue near the pituitary gland. The diabetes insipidus was treated with 2 × 0.05 mg desmopressin (DDAVP) per day. On account of the benign course of the LCH only regular attendance in the outpatient department was indicated. During the first 3 years of follow up, progressive reduction of his growth velocity occurred (Fig. 1a). At 7 years of age his height was 110.0 cm (3rd percentile). GH provocation tests with L-dopa/propranolol and clonidine revealed GH deficiency. Subsequently GH substitution was started with intra-muscular injections of hGH twice a week. Two years later hormone substitution therapy was ceased because of the implication that hGH substitution can lead to the transmission of Creutzfeldt-Jakob disease [4, 11]. In the pre-treatment year the patient grew 3.4 cm, in the 1st year of therapy 10 cm and in the 2nd year 8 cm. After these 2 years his height was between the 3rd and the 10th percentile. In the 1st year thereafter he grew 6.5 cm, which is an accelerated growth velocity for children in the Netherlands [14] and GH provocation tests showed no abnormalities. The onset of puberty was not delayed and at the end of observation, when the patient was 15 years old, his height was 171 cm, which is on the 50th percentile. There has been no evidence of other manifestations of LCH over the total follow up period.

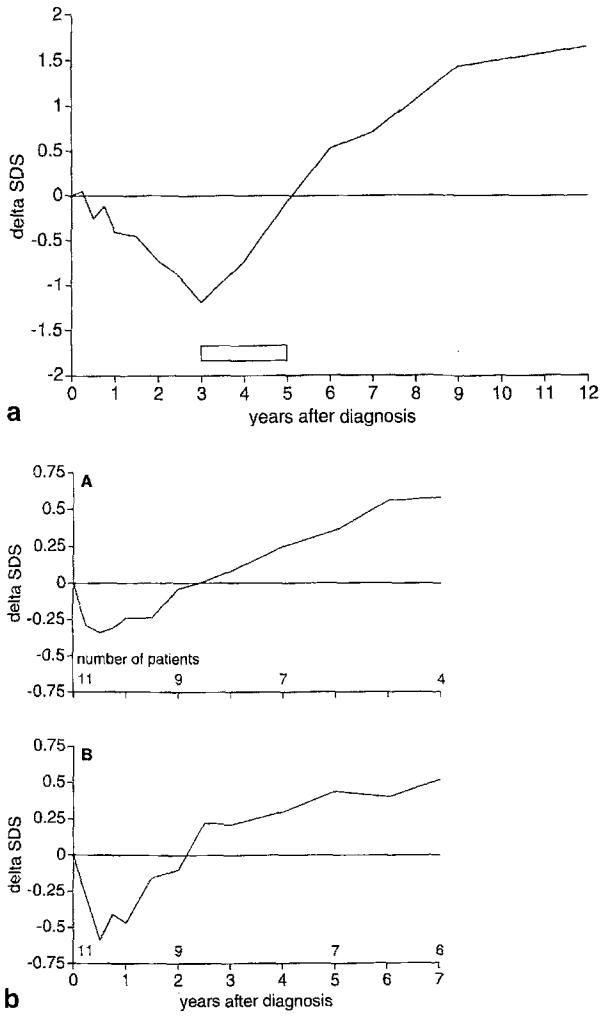

Fig. 1 **a** The delta SDS curve of the patient with LCH and GH deficiency. The period of hGH substitution is indicated. **b** The mean delta SDS curve of patients with isolated LCH (above) and of patients with disseminated LCH

Results

The 22 available patients consisted of 11 boys (mean age 2 years and 1 month) and 11 girls (mean age 3 years and 6 months). Eleven patients had disseminated LCH (mean age 1 year and 10 months, median follow up 7 years and 2 months) and 11 patients had isolated LCH (mean age 3 years and 9 months, median follow-up 6 years and 2 months) [see Table 1].

The mean SDS at time of diagnosis for patients with isolated LCH was 0.04, whereas the mean SDS at time of diagnosis for patients with disseminated LCH was –0.37. Figure 1b shows mean delta SDS-curves of patients with isolated LCH and disseminated LCH; by definition the delta SDS at time of diagnosis is 0. During the first 6 months after diagnosis the mean delta SDS decreased. In the group of patients with disseminated LCH this decrease

Table 1 Incidence of organ involvement for the 22 patients with LCH

	Localized ($n = 11$)	Disseminated ($n = 11$)
Bone lesions	9 (82%)	10 (91%)
Skin lesions	2 (18%)	6 (55%)
Hepatomegaly	–	3 (27%)
Splenomegaly	–	2 (18%)
Pulmonary lesions	–	3 (27%)
Lymphadenomegaly	–	4 (36%)
Diabetes insipidus	–	2 (18%)

was more clear. In the following 18 months the mean delta SDS increased to zero, this is catch-up growth. In the period from 2 years after the diagnosis until the end of the observation period (8 years after diagnosis) mean delta SDS was above zero and is considered overshoot.

Thirteen patients were treated with the mentioned chemotherapeutic regimen, including 4 patients with polyostotic localized disease or with progression of their localized LCH. Two of these 13 received additional radiotherapy. Four patients were treated with radiotherapy only. The remaining 5 patients were diagnosed either with surgery or biopsy and were observed.

Discussion

Literature on long-term growth patterns of children with LCH is scarce. In 22 patients with biopsy proven LCH Dean et al. [6] observed 1 patient, who had received 30 Gy irradiation directly to the hypothalamic-pituitary area, with clinical and biochemical evidence of GH deficiency. GH provocation tests were done in 11 more patients. Despite normal stature and growth velocity three patients (all with diabetes insipidus) showed subnormal GH responses. Their growth rates, however, continued to be normal over 6 to 14 years of follow up. The authors concluded that true growth failure only occurred in association with a direct hypothalamic-pituitary irradiation. Braunstein et al. [2] reported the response of five patients with Hand-Schüller-Christian disease to hGH therapy. In this study the mean growth rate was 7.5 cm in the 1st year of therapy and 5.1cm in the following year. In the pretreatment year the mean growth rate was 2.3 cm. In this study the patients treated with hGH responded well [2]. In a report by Latorre et al. in 1974 [10], 13 children with LCH documented by biopsy were studied. All but one of the children had multisystem involvement and slow, chronic, clinical courses. Ten children had had clinical disease in excess of 8 years at the time of endocrine evaluation, one child for 5 years, and two children for 2 years. Evidence of diabetes insipidus was one of the initial complaints of four children and was manifest in 9 of 13 at the time of this study. Of the 13 patients, 8 were at or below the 3rd percentile for height, 3 were at the 10th percentile, and 1 patient, although above the 50th percentile for height at the time of study, had suffered sustained marked reduction in growth rate during the previous years. Evidence for suboptimal growth was present in 12 of the patients. Diabetes insipidus and/or GH deficiency was present in ten patients [10]. Eosinophilic granuloma in a vertebra, causing vertebra plana, has only a minor influence on final length as the collapsed vertebra reaches at least 80% of the height of the adjoining vertebra after recovery [12]. This sequelae will only lead to a decrease of length of a few centimetres if more than one vertebrae are affected.

Two of our patients were suspected to have GH deficiency. GH provocation tests revealed that one patient had developed GH deficieny as a complication of LCH. This patient was treated with hGH for 2 years and responded well. After ceasing the therapy, the GH provocation tests showed no abnormalities. The patient continued to grow at an accelerated rate and consequently reached the 50th percentile. It is known that spontaneous remissions can occur in LCH [3, 5]. A spontaneous remission of the LCH lesion in the pituitary gland and/or hypothalamus can be the explanation in our patient for his normal provocation tests and accelerated growth after ceasing the hGH therapy. This accelerated growth velocity could indicate that growth velocity was already lowered before primary diagnosis.

Although a small group the incidence of affected organs of our patients with disseminated LCH is comparable to the literature [7]. The delta SDS curves of the group of patients with isolated versus disseminated LCH (Fig.1b) show a similar course. However, in the post diagnosis period the SDS of patients with disseminated LCH becomes more negative. The explanation for this larger reduction in growth velocity can be that patients with disseminated LCH are more severely affected and accordingly, therapy is more aggressive. In spite of continuation of therapy, the catch-up growth begins 6 months after diagnosis. Two years after diagnosis the delta SDS becomes positive until the end of observation. This overshoot could be explained by assuming that reduction in growth velocity could have appeared before the diagnosis is made. Thus in reality this overshoot may be a return to the initial percentile.

The delta SDS curve of patients treated with chemotherapy is comparable with delta SDS curves of patients with (non high-risk) acute lymphoblastic leukaemia treated with chemotherapy without radiation therapy [8]. However in these patients the delta SDS diverges to zero after 5–6 years of overshoot. Craniospinal radiation of 24 Gy or more can cause reduction of GH secretion [8, 13]. In our group one patient received 24 Gy to the pituitary gland region, but did not develop GH deficiency.

It is striking that ten patients did reach a percentile clearly higher than their percentile at diagnosis. All had

one or more lesions on the facial side of the skull. An explanation for this phenomenon remains uncertain, but one can speculate that the GH release of the pituitary gland is elevated after recovery of the LCH, or decreased before LCH is diagnosed. No data of height were available before the diagnosis of LCH was made.

In summary, GH deficiency is not a common manifestation of LCH in childhood and GH provocation tests are only indicated when there is a poor or decelerating growth rate. Height of LCH patients at diagnosis does not differ from the average height of a healthy population. We found that no growth retardation occurred under influence of the number of organs involved and/or therapy in all patients but one.

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