Growth hormone treatment in pituitary insufficiency: selected cases of children with craniopharyngioma and medulloblastoma

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Abstract

Purpose: The work concerns the substitution treatment with growth hormone (GH) in hypopituitary children, including cases that occurred in the course of tumor disease, craniopharyngioma (CP) and medulloblastoma (MB).

Material and methods: The studied population concerned 117 children who presented either somatotropic or polyhormonal pituitary insufficiency (the average age was 12.6 years for girls and 13.6 years for boys). The diagnosis of somatotropic pituitary insufficiency (SPI) was based on insulin and clonidin stimulation tests evaluating GH reserve of hypophysis. The computer tomography (CT) and nuclear magnetic resonanse (NMR) examinations were carried out before GH substitution in all children. The tumors (four CP cases and one case of MB) were all found in boys and they were treated with surgery and/or radiotherapy. All studied children, including CP and MB operated patients were treated with human GH (hGH) – Genotropin 16 IU, administered in subcutaneous injections. The daily dose was calculated as 0.5 IU/kg/week.

Results: The annual increase of children height before GH therapy was about 3.2 cm. In the first year of GH therapy the difference in children growth between the CP/MB group as compared with the rest of patients was less than 1.0 cm: 9.4 and 10.2 cm/year, resp. During the second year of hormone substitution the growth became slower: average values were 8.2 cm and 7.4 cm/year, resp. In CP and MB patients the height increase calculated as SDS values was significant (2.7 and 1.0 resp.). Control NMR examination performed in CP/MB patients treated with surgery with subsequent hGH therapy did not demonstrate any recurrence of tumor.

Conclusions: After two years of hGH therapy the final heigth of hypopituitary children, including CP patients, nearly reached the values observed in healthy children. GH therapy did not induce a recurrence of neoplasm in CP and MB patients.

Key words: growth hormone, pituitary insufficiency, craniopharyngioma, medulloblastoma.

Introduction

The growth retardation and deficit in height uncorresponding to the age constitute physical as well as psychological problems for children and young adults [1,2] commonly leading to negative social and professional effects [3,4]. The problem becomes particularly important if the underlying tumor disease occurs [4].

In the current paper, we studied population composed of hypopituitary children. The insufficiency of the anterior pituitary gland was treated with human growth hormone [5,6]. During the treatment, the CT scans showed in some children the presence of tumor, either CP [7,8] or MB [9,10]. CP is usually localized in the suprasellar region. It can also occur, especially in children, as intrasellar lesion [8]. CP is related to the multiple hormonal deficiency known as hipopituitarism [7]. Medulloblastoma is an invasive embryonal tumor of the cerebellum with an inherent tendency to disseminate via cerebrospinal fluid (CSF) pathways [9,10].

The detected tumors appeared as the reason of existing hypopituitarism. We have analyzed the effects of hGH treatment in the tumors bearing children population.

According to literature [11-13], hGH substitution should be ordered in all cases with apparent GH deficiency regardless of the child's height. Our CP and MB patients showed GH deficiency, thus they were all treated with hGH. In addition, the question if the children suffered from pituitary insufficiency

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combined with neoplasm disease should or should not be treated with GH, was largely discussed in the study.

The physiological mechanism of GH action is closely related to insulin-like growth factor-1 (IGF-1) effects [6,14,15]. IGF-I is known as one of the principal factors responsible for tumor initiation and proliferation [16-19]. For this reason, in CP and MB cases mentioned above, the existing tumors were eliminated by surgery followed by radio- and chemiotherapy, just before GH therapy. However, we cannot completely eliminate the risk of tumor reccurence, especially after treatment with hGH.

Material and methods

The population of 117 children (33 girls and 84 boys) was studied. The age was 4.6-18.1 years (the average age was 13.6 years for boys and 12.6 years for girls). All children presented isolated somatotropic pituitary insufficiency (SPI, n=79) or polyhormonal pituitary insufficiency (n=38).

In all studied children, head CT (Siemens Somatom HiQ) examination was carried out before GH substitution. In any case of CT image interpretation problems the NMR (Siemens Magnetom Impact 1 Tesla) examination was additionally performed. The children with recognised tumor disease were submitted to the surgery with subsequent pathological examination.

The diagnosis of SPI was based on two different stimulation tests which evaluated GH reserve of anterior pituitary gland [20,21]: 1) insulin (I.V, 0.15 U/kg of body mass) and 2) oral clonidine (150 μg/m^2 of body area) were used as stimuli. The timing for blood collection to test GH levels was following: 0, 30, 60, 90, 120 min (both tests) and then 150 and 180 (clonidine test) [20-22].

The hormone serum levels were quantified by radioimmunoassays for: GH, TSH, free T4 (Microparticle Enzyme Immunoassay, MEIA, Abbott Laboratories) and cortizol (RIA, Radioimmunoassay, Biochem Immuno Systems). The LH and FSH anterior pituitary secretion was estimated by LH-RH test [20,21] and their levels were quantified with use of the appropriate kit (MEIA, Abbott Laboratories). The serum IGF-1 level was detected before and after surgery by radioimmunoassay.

The patients were treated with subcutaneous injections of hGH, Genotropin 16 IU (Pharmacia-UpJohn), using GenotropinPen 16 IU. Human GH was administered every night just before sleeping. The dose was calculated as 0.5 IU/kg/week.

Growth was measured by Holtain standiometer, and growth deficit was assessed by height standard deviation score (SDS). The growth termination was defined as annual growth less than 2 cm and by knitting of long bones epiphysial plates (bone X rays of undominating upper extremity). The bone age was evaluated by Gruelich-Pyle method [23].

Results

Mean metric age (MA), at the diagnosis of pituitary insufficiency and GH therapy involvement was 13 years (12.6 years in girls and one year more, i.e. 13.6 years in boys).

Table 1. Pretreatment characteristics of the children/youth group with somatotropic or polyhormonal pituitary insufficiency, included in the study.

	n	MA	BA	Growth retardation (MA-BA)
Girls	33	12.6	8.3	-4.3
Boys	84	13.6	9.7	-3.9
Average	-	13.0	9.0	-4.1
Together	117			

MA, metric age; BA, bone age

At the diagnosis bone age (BA) was remarkably delayed as compared with MA. The average retardation was of about 4 years and was more evident in girls (-4.3y). BA deficit in boys was -3.9y, the difference is not significant. The particular data was summarized in the *Tab. 1*.

The average annual growth rate measured during the last half year before treatment amounted 3.2 cm and was a little higher for boys then for girls (3.4 cm and 2.9 cm, resp.). Prepubertal female patients grew distinctly slower than girls with puberty signs. This difference was practically absent for boys (*Tab. 2*).

During the first six months after GH involvement, growth was visibly accelerated and reached 10.4 cm/y for boys and 10.5 cm/y for girls, on average. In the second half-year the growth rate in both sex slightly decreased, the average values were 10.0 cm/y for girls and 9.9 cm/y for boys. The difference in growth rate dependent on prebubertal vs pubertal age observed in the first year of treatment was considered as not significant. In the consecutive years the growth rate became retarded, particularly for girls (*Tab. 2*).

In 6 children, the CT examination revealed the eminent anatomic lesions responsible for altered hormone secretion [24]. In other 8 cases, CT scans showed the pathological image of hypophysis and other central nervous system areas and were completed then by NMR. In 6 cases of this group the presence of tumor was recognised.

The NMR detected tumors were removed by surgical treatment. The subsequent tumor pathology demonstrated the presence of neoplasm in 5 cases (in the last child the lesion was not neoplasm).

The final diagnosis established in five children, all boys, was one case of medulloblastoma (MB) desmoplasticum, that infiltrated the chamber IV, and four cases of craniopharyngioma (CP), with both, supra- and intrasellar localization. The boy with MP (4 years old) was treated with surgery followed by radio- and chemiotherapy. For two boys with CP (14 years old both), the surgery was completed by subsequent radiotherapy. For the other two boys the surgical treatment was sufficient enough.

The data concerning the serum level of secreted hormones are presented in the *Tab. 3*. The deficient GH secretion was demonstrated in all patients. The baseline IGF-I level in children with tumors was increased and it has strongly declined after surgery, just below the age normal value limit. The sec-

Table 2. The growth rate of hypopituitary patients before the hGH substitution and during the first two years of the treatment.

Sex	Prepuberty growth rate (cm)				Growth rate during puberty (cm)			
	before hGH therapy	The time of hGH therapy			Before hGH therapy	The time of hGH therapy		
		0–6 months	6–12 months	2nd year		0–6 months	6–12 months	2 nd year
Girls	2.4	10.8	10.1	7.2	3.4	10.1	9.9	6.2
Boys	3.4	10.6	9.6	7.8	3.4	10.2	10.3	8.6

hGH, human growth hormone

Table 3. Hormonal disturbances in CP/MB children included in the study.

No	Diagnosis	SPI	HT	GD	CPI	ACI
1.	CP	+	+	+	+	+
2.	CP	+	+	+	+	+
3.	CP	+	+	+	-	+
4.	CP	+	+	-	-	-
5.	MB	+	+	-	-	-

SPI, somatotropic pituitary insufficiency; HT, hypothyreosis; GD, gonadotropin deficiency, CDI, central diabetes insipidus; ACI, adrenal cortex insufficiency

Table 4. The growth of CP and MB patients treated with GH after surgery.

No	Diagnosis	Growth before hGH therapy (cm)	Growth during hGH therapy (cm)			
			0-3 months #	3-6 months #	6-12 months #	2nd year
1	CP	3.0	8.1	9.0	8.0	7.3
2	CP	3.6	9.45	9.35	9.0	7.4
3	CP	4.2	10.9	9.7	10.1	7.5
4	MB	1.8	9.4	9.0	9.2	--

CP craniopharyngioma; MB medulloblastoma; hGH human growth hormone.
Results recalculated as annual growth

ondary hypothyreosis was recognized in all these patients, additionally in two CP boys the central diabetes insipidus appeared. The adequate substitution treatment (with thyroid hormones and Adiuretin, resp.) was introduced. In three children with CP the gonadothropin deficiency was found. For these patients, the need of hydrocortisone replacement therapy occured.

The children with CP were treated with GH during 1-1.7 years after surgery. In one CP boy the parents did not agree to treat their child with hGH (so the study concerned only three CP patients). In the case of MB the GH treatment started 8 years after surgery.

The data on the growth of GH treated children were presented in *Tab. 4*. The children grew relatively faster in the first year of the substitution therapy, especially at its beginning, than during the second year of treatment (about 9.4 cm/year and 7.4 cm/year, resp.).

Actually two patients after craniopharyngioma radical surgical treatment has already finished their GH treatment; the boys are 166 and 178 cm tall. Their growth SDS values increased during the treatment from -4.1 to -0.52 and from -1.6 to +0.1, resp. The boy with removed medulloblastoma with pretreatment SDS value of -3.4, responded to the replacement therapy with relatively rapid growth: his SDS value was -2.41 after one year of treatment (*Tab. 2*).

Control NMR examinations carried out in all GH treated patients did not reveal any recurrence of neoplasia.

The growth data of all studied groups treated with hGH, i.e. CP/MB group vs the group of patients free of tumor disease (non-tumor, NT), were presented in *Tab. 5*.

Discussion

The comparison of GH treatment of non-tumor and CP/MB tumor patients, both with SPI was limited in our study to the male sex; the girls were not taken into consideration. By the way, the maturation did not affect the growth results obtained in boys before and during GH therapy, especially during the first year of treatment.

On the other side, the height increase in CP/MB patients, as compared with the non-tumor (NT) children did not show any difference before GH treatment. On the contrary, the dif-

Table 5. The growth of CP/MB patients and "non-tumor" male patients treated with hGH after surgery.

No	Diagnosis	Anual growth before hGH therapy (cm)		Growth during hGH therapy (cm)					
				0-6 months #		6-12 months #		2nd year	
1	CP	3.0		8.6		8.0		7.3	
2	CP	3.6	3.6*	9.4	9.4*	9.0	9.0*	7.4	7.4*
3	CP	4.2		10.3		10.1		7.5	
4	MB	1.8		9.4		9.2		–	
5	NT	3.4		10.4*		9.8*		8.2*	

CP craniopharyngioma; MB medulloblastoma; NT non-tumor patients; hGH human growth hormone
* mean values
# Results recalculated as anual growth

ference seemed to appear during the first year of substitution therapy, especially in the first six months of GH treatment, i.e. the NT children were growing relatively faster; however, the maximal growth difference found during the first six months of therapy did not exceed 1.0 cm. Before GH therapy the growth rate in CP patients, as compared to NT group, was higher and statistically significant. Later, during GH treatment, the rate of growth became similar in both groups. These observations showed that the appearance of craniopharyngioma as the cause of pituitary insufficiency in children did not affect considerably the results of GH therapy.

GH deficiency is present in 72% of CP children, however the reduced height in CP children is observed after surgery only in 53% of cases [25]. Due to literature data, in some operated cases the children with prior GH deficiency developed hyperphagia and obesity. They grew as "healthy" children and revealed the increase in insulin secretion, the phenomenon that can explain the normal IGF-1 level [7,12,26]. However, some authors [12,13] suggest that these children, despite their normal growth, should be treated with GH because of metabolic alterations.

CP patients treated with surgery and radiotherapy may even present the exacerbation of the prior metabolic disturbances [27]. Any way, the study presented by de Vile and al. [28] showed that surgery increased the extent of existing panpituitarism from 71% to 75% only. According to other researchers, the SPI was observed in 90-100%, hypothyreosis in 64% and diabetes insipidus in 13% of CP patients in the preoperative period [29,30]. However, according to the cited authors, the surgery enhanced the frequency of diabetes two fold and additionally caused gonadotropin deficiency in all patients.

Similarly to our results concerning the presence of SPI and gonadotropin deficiency after surgery in CP patients, some authors observed SPI in 100% and gonadotropic deficiency in 50 % of treated cases (in our results 60%). Moreover they found hypothyreosis in 62.5% and corticotropic insufficiency in 75% of cases [8]. In our study corticotropic insufficiency occured only in 60% of treated patients, however, the diapedes insipidus was more frequent (50%).

We admit in principle the GH substitution after CP or MB surgery. However, after this type of therapy we can not exclude the risk of tumor reccurence. The study performed in England by Swerdlow et al. [31] showed that among 100 adult CP patients after surgery followed by hGH therapy, only in one person a new neoplastic proliferation appeared and it was finally stopped during treatment [32]. In another study that included 180 English children with CNS tumors treated with surgery, radiotherapy and subsequent hGH substitution, no new tumor process was observed. Kanev et al. [33] confirmed the low risk rate showed by Swerdlow.

On the other side, Uchino [11] has showed, that among 25 children treated with hGH, the neoplastic disease has reappeared in four patients – two of CP, one of astrocytoma and one of germinoma. In cells of craniopharyngioma, the author demonstrated the presence of GH receptor, thus he explained the possible increased risk of neoplastic growth as the undiserable side effect in this type of therapy.

Kranzinger [34] has described the 14 year old girl with CP, treated by surgery, radiotherapy and GH replacement. Four years later an astrocytoma occurred. Other twelve similar cases were also described [34]. However, it seems quite possible that the astrocytoma proliferation was caused rather by radiotherapy than by GH treatment. Moreover, the reappearance of neoplasia was found generally in patients treated only with surgery and without subsequent radiotherapy [35].

According to the published data concerning 422 children with CP treated with surgery and hGH substitution (Kabi International Growth Study, KIGS Database) [12], the neoplastic process reappears in 13.6% of cases, in a average four years after surgery and two years after hGH therapy. Nevertheless, hGH therapy seems to be useful for evident reason of child growth and GH-related metabolic mechanisms [12]. Moshang et al. [35] demonstrated that in studied population of 1262 cases only 6.6% of children with CNS tumors treated by surgery and hGH replacement showed the tumor "come back", commonly in glioma and medullobastoma cases; the authors suggest that the risk of CP and other CNS tumors reapparance is much lower in children treated with both surgery and hGH than with surgery alone [36]. For example, Cowell and Dietsch [Cowell], have published data of patients treated with hGH showing that CP and other CNS tumors reappeared only in 3.8% and 2.2% cases, respectively (and the leukemia apperance rate in the same group was 1.1%). The authors conclude that neoplastic reccurence frequency is identical in hGH treated and untreated patients [37].

The most important effect of hGH therapy in CP children was the growth acceleration observed in this group, the result which could be compared to the parallel effects of the same

therapy applied to children with idiopathic GH deficit [12,35]. Our results obtained in CP patients have to be compared with those of Price et al. [12,35] and Hogeveen et al. [38]. In the study of Hogeveen the two years of hGH therapy diminished the GH deficit up to SDS value -0.9. In the studies of Price et al. [12,35] the growth of treated CP children reached the values not far from the average values of healthy population: -0.71 SDS. Price and Jonnson [12] consider that hGH therapy allows in CP patients to increase SDS of growth up to 1.5. In our study in CP patients treated by hGH, growth deficit assessed by height standard deviation score (SDS) was reduced in two cases up to -0.52 and +0.1. SDS of growth increased as much as 2.7 (statistically $p<0.001$) and it was the reason for the final height of our CP patients after two years of hGH therapy which approached the values characteristic for "normal" children.

On the contrary, according to Price et al. [39] the effect of hGH therapy in other CNS tumors was less spectacular than in CP patients. By the way, other researchers consider that in 20--30% of hGH treated CP children the growth is more delayed than in healthy population. However, this observation concerns mainly the treated girls [28,40]. Herbert et al. [40] were even less successful, as they found the positive results only in 44% of CP cases. Moreover, the patients' growth was less evident if radiotherapy was used in CP and other CNS tumors [28]. Kanev et al. [33] suggest that the approach to the "normal" growth in hGH therapy cases depends on the start point of the treatment: the earliest the treatment is started, the better the effect are. Price et al. [35,39] have also observed that the deficit of final height correlates with the growth deficit before treatment and the moment of hGH therapy onset.

As to the case of our medulloblastoma patient treated with hGH, despite the fact that radiotherapy was also used, his growth was practically identical with the one of our CP treated patients. After one year of hGH therapy, height SDS rose from -3.4 μp to -2.4, so the increase in height observed in this boy (1.0 of SDS values) was statistically significant ($p<0.001$). The last observation is to be compared with similar growth acceleration events observed after one year of hGH therapy in CP patients studied by Hogeveen [38]. Nevertheless, as it was mentioned above, Price considers that the positive results obtained in CP patients do not concern other CNS tumors [39].

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