

Final Height in Children with Medulloblastoma Treated with Growth Hormone

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Key Words

Medulloblastoma · Growth hormone · Therapy · Index of responsiveness · Final height

Abstract

Background: Medulloblastoma is the most frequent primary solid central nervous system tumour in children. The 5-year survival rate is at present at about 60%. Height in general is severely compromised in survivors. The present study is an extension of the investigation by the author's group of the effect of exogenous growth hormone (GH) among medulloblastoma patients. **Methods:** A total of 113 patients with medulloblastoma (out of 682 cases documented in KIGS, Pfizer International Growth Database) were treated with GH till final height was achieved. At the start of GH therapy (median dose 0.18 mg/kg/week), patients were 8.9 years old and had a median height SDS of –1.6. **Results:** After 6.8 years of GH, final height SDS was –1.9, reflecting an overall loss in height of 0.3 SDS. This contrasted with an age-matched group of patients with idiopathic growth hormone deficiency (iGHD, n = 1,986), whose gain in height was 1.6 SDS on the same dose. The index of responsiveness averaged –0.9 during the first prepubertal year and –2.0 during total pubertal growth, thus indicating a major im-

pairment in responsiveness to GH as compared to iGHD. Height at GH start, which correlated positively with the age at disease onset, was found to be the major determinant of final height. **Conclusions:** Our findings show that attempts to improve the height outcome in medulloblastoma must involve earlier recognition and treatment with higher-than-replacement doses of GH; additionally, modifications in cancer treatment programs need to be considered, such as lowering the dose of craniospinal irradiation or avoiding it as far as possible.

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Primary tumours in the central nervous system (CNS) are the most common malignancies in childhood, apart from leukaemias, and have an incidence of 24 among 1,000,000 children <15 years of age [1]. Medulloblastoma is the most frequent primary solid CNS tumour in children, accounting for 10–20% of CNS neoplasms and for about 40% of all tumours within the posterior fossa [2–4].

Current treatment for medulloblastoma involves primary operative debulking to reduce tumour size and to confirm the pathologic diagnosis; craniospinal irradiation (CSRT) follows, with dosage dependent upon local or national protocols. Adjuvant chemotherapy includes varied

agents. The 5-year survival rate is at present at about 60%, but is lower in children under 3 years [5–7]. Unfortunately, height in general is severely compromised in survivors, whether children, adolescents or adults, particularly if the child was very young at the time of diagnosis [8–10]. Spinal irradiation leads to disproportionate short stature, with an associated decrease in sitting height [11]. The dosage of CSRT has a substantial impact on height growth [12, 13]. The cause of the height impairment is attributable to a combination of growth hormone (GH) deficiency (GHD) and impaired sensitivity of growing tissue to growth-promoting factors, and, primarily, radiation osteitis of the vertebral column. Few reports are available on the effect of exogenous GH [12–15], and it was concluded that the long-term benefits of GH treatment were rather negligible. In 1999, the author's group [16] analyzed 350 medulloblastoma patients documented in KIGS (Pfizer International Growth Database), and a subpopulation of 43 individuals who had been treated till adult height was reached. The aim of the present study is to expand our previous report by evaluating follow-up data with particular emphasis on adult height assessment.

Patients and Methods

The KIGS database is an international registry developed with the main objective of documenting the long-term outcomes and safety of Somatomorm and Genotropin, both GH products (Pfizer, Inc., New York, N.Y., USA). The KIGS survey is conducted in accordance with the recommendations adopted by the 18th World Medical Assembly (in Helsinki, Finland, in 1964) and subsequent revisions, which exist to guide physicians carrying out biomedical research involving human individuals. Each subject and/or his/her legal representative receive adequate information, have the right to withdraw from the survey at any time, and consented to his/her participation. In contrast, this kind of registry or non-interventional trial that KIGS represents did not require informed consent from the subjects or legally acceptable representatives in many countries during the first decade of its existence. Currently, informed consent is required and the anonymous use of the data complies with rigorous privacy guidelines.

Our analysis of these patients involved the dataset available up to March 19, 2004. Medulloblastoma was classified according to the KIGS coding system (Code # 2.2.2.4) [17]. The dataset does not include patients from North America as such were not treated long enough with Pfizer GH to achieve final height. The patients were carefully monitored during treatment to assure that they were euthyroid.

Standard deviation scores (SDS) for height were based on the standards of Tanner et al. [18]. Height velocity for chronological age was only calculated when two consecutive height measurements had been documented during a 9- to 15-month period. Size at birth (SDS) was estimated by using the standards of Niklasson et al. [19].

Weight and body mass index SDS was calculated according to the British reference data of Freeman et al. [20]. The sitting height ratio was defined as sitting height (cm)/standing height (cm), which was based on the reference data of Gerver and De Bruin [21]. Methodology for determination of sitting height was similar in the clinics which provided data for the KIGS database. Bone age estimations were done by the referring physicians, who applied the standards devised by Greulich and Pyle [22]. Age at onset of puberty was defined as the first visit at which Tanner breast stage 2 (B2), unbiased by exogenous estrogens, was documented in girls; in boys it was marked by a mean testicular volume of >3 ml. Additionally, as some patients may have impaired growth of seminiferous tubules due to irradiation, evidence of systemic androgenization contributed to the pubertal assessment. Inclusion criteria required that the transition from a prepubertal to pubertal status was documented within a period of <6 months. Mid-parental height (MPH) SDS was calculated according to the equation: (HT SDS father + HT SDS mother): 1.61 [23]. Near-final height was assumed when height began to slow down progressively and height velocity was <2 cm/year or when bone age was \geq 14 years in girls and 16 years in boys, respectively.

In a subset of prepubertal children (boys <11 years; girls <10 years), we compared height velocity during the first year of GH treatment with the height velocity prediction values based on the model for prepubertal children with idiopathic GHD (iGHD) [24]. Total pubertal growth (TPG) from appropriate patients was compared with TPG in adolescents with iGHD [25]. Differences between observed and predicted heights were expressed in terms of Studentized residuals (SRs). The residuals are calculated according to the formula: observed height velocity – predicted height velocity for each observation and the SR is the residual divided by its SE. This 'index of responsiveness' represents the degree to which the actual growth does or does not exceed the prediction. In order to compare the data with the total group of patients with medulloblastoma, we analyzed a group of children with iGHD (Code # 1.ff) in KIGS [17], who matched the medulloblastoma group for age, for the duration of GH replacement and had been treated to final height (n = 1,986).

Statistical Analysis

Wilcoxon rank tests were used for comparisons, median values, and 10–90th centile ranges. The Spearman correlation coefficients are quoted, and p values correspond to two-sided tests. In addition, mean and SD values are given if appropriate. For multivariate regression analyses, the procedure REG in the program package SAS® Version 8 was used.

Results

In the KIGS database, the total number of patients with medulloblastoma was 682 (452 being male), and 113 (71 males) of them had reached near adult height. The characteristics of these patients as well as of the comparable group with iGHD (n = 1,986; 1,231 males) are listed in table 1. The median age at primary diagnosis was 6.3 years. In the total group of medulloblastoma patients,

Table 1. Patients with medulloblastoma (n = 113, male 63%) and iGHD (n = 1,986, male 62%) treated with GH to near adult height

Variables	Medulloblastoma			iGHD			p <
	Median	10th	90th	Median	10th	90th	
Background							
Birth weight (SDS)	-0.1	-1.5	1.1	-0.7	-2.1	0.8	0.001
MPH (SDS)	0.3	-1.3	1.5	-0.7	-2.3	0.9	0.001
Maximum GH, $\mu\text{g/l}$	4.8	1.7	12.3	4.8	1.0	8.9	n.s.
Age at primary disorder	4.5	1.7	9.6	-	-	-	
Start of GH treatment							
Age, years	8.9	5.3	12.0	9.4	4.6	12.7	0.01
Height (SDS)	-1.6	-2.8	-0.2	-2.7	-4.2	-1.8	0.001
Weight (SDS)	-1.1	-2.5	0.3	-2.3	-4.4	-0.8	0.001
Sitting height (SDS)	0.0	-1.2	0.9	0.4	-1.1	1.8	0.001
Dose GH, mg/kg/week	0.18	0.12	0.23	0.19	0.13	0.29	n.s.
First year of therapy							
	(n = 92)			(n = 1,597)			
Height velocity, cm/year	7.9	5.2	10.1	8.2	5.9	11.9	0.001
Δ height (SDS)	0.4	0.0	0.8	0.5	0.1	1.3	0.001
Studentized residual	-0.9	-2.0	0.5	0.0	-1.2	1.6	0.001
Onset of puberty							
	(n = 44)			(n = 802)			
Age, years	12.0	9.8	14.7	12.9	11.1	15.6	0.01
Height (SDS)	-1.2	-2.5	0.1	-1.0	-3.0	-0.3	0.01
Sitting height (SDS)	-1.3	-3.2	0.6	0.5	-1.0	1.9	0.001
Dose GH, mg/kg/week	0.18	0.14	0.23	0.19	0.13	0.24	n.s.
Latest visit							
Age, years	17.3	15.5	19.1	17.5	15.3	20.0	n.s.
Height (SDS)	-1.9	-3.7	-0.1	-1.1	-2.7	0.3	0.001
Weight (SDS)	-1.1	-3.0	1.1	-0.8	-2.7	1.0	0.01
Sitting height (SDS)	-2.0	-3.7	-0.4	0.7	-1.2	2.3	0.001
Total Δ HT (SDS)	-0.3	-1.4	1.0	1.6	0.3	3.4	0.001
Years on GH	6.8	4.8	10.9	7.5	4.7	12.5	0.01
Stud Res TPG	-2.0	-4.4	-0.4	0.1	-1.3	1.5	0.001

Height velocity calculations are based on two height measurements (9–15 months apart).

96% received cranial irradiation, 80% spinal irradiation and 62% chemotherapy. The median maximum GH level measured during GH stimulation tests was 4.8 $\mu\text{g/l}$. Our data further showed that, in the NAH group comprising 113 patients, the following disorders occurred: 53% TSH deficiency, 22% gonadotropin deficiency, 9% ACTH deficiency, and 1% ADH deficiency. Weight at birth (-0.1 SDS) and MPH (0.3 SDS) were close to the population average. Age at GH start was 8.9 years, with a height SDS of -1.6, and a sitting height SDS of 0.0. The starting GH dose was 0.18 mg/kg/week and the same order of magnitude was maintained during treatment.

During the first year of GH treatment (n = 92) we observed a height velocity of 7.9 cm/year, which corresponded to a Δ height SDS of 0.4 SDS. At the onset of puberty

(n = 44), at an age of 12.0 years, our findings showed a height SDS of -1.2 and a sitting height SDS of -1.3.

Characteristics such as birth weight, MPH, maximum to GH tests, age at GH start, height SDS at GH start, first year growth and the age at onset of puberty did not differ between the children who did or did not receive spinal irradiation.

At 17.3 years of age and after 6.8 years on GH, height SDS was -1.9, showing an overall loss in height SDS of -0.3 from the time GH treatment started. Weight SDS remained constant from the beginning to the end of treatment. Sitting height SDS declined from -0.0 to -2.0 SDS, the decline mainly occurring during puberty. We did not observe significant differences between those who received or did not receive spinal irradiation.

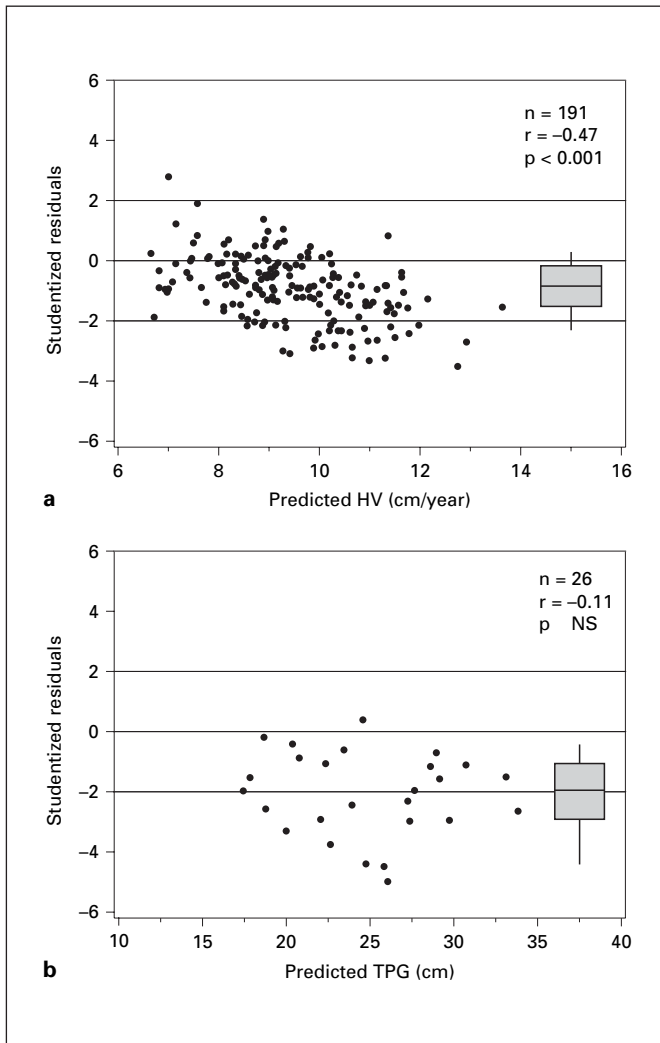


Fig. 1. a The Studentized plot (Studentized residuals vs. predicted height velocity) for the first year of GH treatment in children with medulloblastoma at near-adult height (based on the prediction model [22] for iGHD without maxGH levels in provocation tests) shows a reduced responsiveness to GH. **b** The Studentized plot (Studentized residuals vs. predicted height velocity) for total pubertal growth during GH treatment in children with medulloblastoma at near-adult height (based on the prediction model [23] for iGHD) shows reduced responsiveness to GH.

As compared to the iGHD group, parental height, birth weight, height and weight at initiation of GH treatment and sitting height were higher in medulloblastoma. Even though the GH dose was similar during the first year of GH, height velocity and gain in height as well as responsiveness to GH, as expressed by the SR, were significantly lower among medulloblastoma patients (-0.9) than in iGHD (-0.2) (fig. 1). Age at puberty onset was also

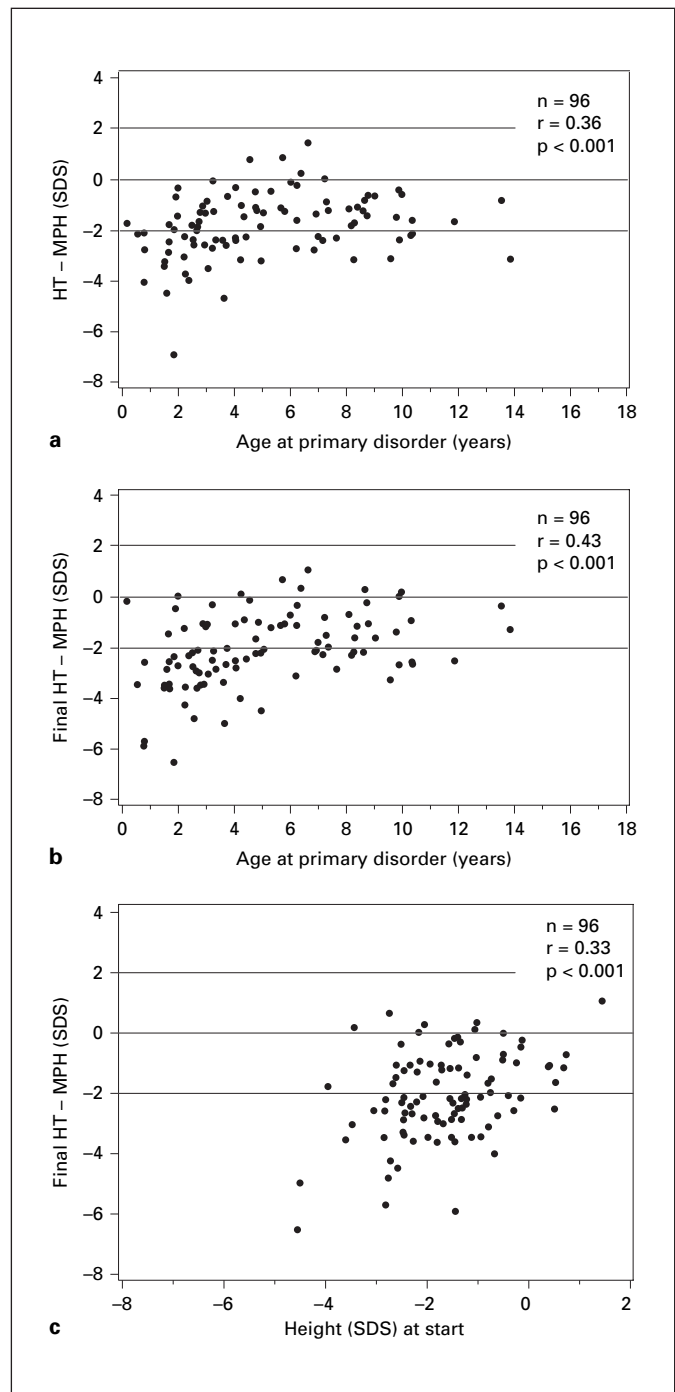


Fig. 2. a Height SD score corrected for midparent height (height SDS – MPH SDS) (y-axis) at the start of GH therapy, depicted in relationship with age at the time treatment of the primary disorder started (x-axis). **b** Final height SD score corrected for midparent height (height SDS – MPH SDS) (y-axis) in relationship to age at the time treatment of the primary disorder started (x-axis). **c** Final height SD score corrected for midparent height (height SDS – MPH SDS) (y-axis) in relationship to height SDS at start of GH therapy.

significantly lower in the medulloblastoma group. Among the boys for whom exact documentation of the onset of puberty was available, the median age was 12.0 years, while it was 11.1 years in the girls. The corresponding figures for iGHD were 12.8 years in boys and 12.0 years in girls.

At the time near adult height was reached, both groups of patients were of the same age and had been treated for a similar number of years. However, children with iGHD were significantly taller, had gained more height, weighed relatively less in relation to their height and had a greater sitting height. Children with medulloblastoma had a loss of 0.3 SDS during the course of treatment in contrast to the gain of 1.6 SDS in iGHD. The SR for TPG was markedly reduced in comparison to iGHD (median -2.0 vs. 0.1) (fig. 2).

In the group with medulloblastoma, final height correlated positively with age at the time the primary disorder was diagnosed (the older the patient, the better). Likewise, final height correlated positively with height at the start of GH therapy. In a multiple regression analysis of the cohort of patients followed up to final height, the following equation was derived ($n = 110$; $R^2 = 0.632$; $p < 0.001$): final height [SDS] = $-3.19 + (\text{height at GH start [SDS]} \times 0.78) + (\text{age at primary disorder [years]} \times 0.07) + (\text{number of injections per week} \times 0.34)$. GH dose did not play a role in this descriptive equation.

Discussion

KIGS is a pharmaco-epidemiological survey and the data are analyzed according to the information provided by the reporting investigators. The age spectrum at the time of primary diagnosis [3], the male to female ratio [26], as well as the modalities of treatment, suggest that the KIGS cohort we analyzed is representative. Treatment in our series of medulloblastoma patients consisted of surgery – often an extended biopsy – followed by X-ray therapy, either cranial (88%) or with added spinal irradiation (71%) and, in approximately 40%, chemotherapy. This combined regimen results in an overall survival rate of about 50%. As a result of the malignancy and of treatment in general, physical and neuropsychological long-term sequelae are common in surviving children [27–29]. A loss of cognitive and intellectual functioning is frequently observed [30]. In addition, most children experience stunting of growth, particularly of the trunk, and attain an adult standing height of between -2.9 and -5.0 SDS [9, 15, 28]. Impaired growth in children surviving medulloblastoma has been attributed to a combination of adverse factors [31, 32]. Even though

X-ray therapy is not directed towards the hypothalamic-pituitary area, impaired GH secretion is commonly observed and occurs in direct relationship to the dose of cranial irradiation and the time elapsed after survival [33, 34]. Defects of other pituitary hormones, such as TSH and gonadotrophins, were reported as a rare occurrence [35–38], a finding which is at variance with our investigations of the KIGS cohort. Less severe radiation to the hypothalamus may lead to an earlier onset of puberty [8, 9], a finding supported by our analysis. Precocious puberty, however, also appears to be rare.

Irradiation of the cranium and the spinal region results in damage to growing tissue, primarily vertebral radiation osteitis. Thus, adult height in survivors of medulloblastoma has been reported to be severely impaired, in particular among children with early onset of the disease and those with high-dose spinal irradiation [12, 13]. Consequently, attempts have been made to treat these children with GH [9, 14–16, 39, 40]. Although pituitary GH was initially given three times per week, daily injections of recombinant human GH have become common practice in recent years. The GH dosage is comparable to that given to patients with iGH deficiency.

Relatively small numbers of children with medulloblastoma who were treated with GH were followed up to near-adult height. In general, ages at initiation of treatment have been similar to or slightly later than our current group. Sulmont et al. [14] reported 27 cases with medulloblastoma who were treated with pituitary GH on a dose of 0.1 – 0.2 mg/kg/week given in three weekly injections. The overall height response during 3.4 years of GH treatment was a loss to adult height of 1.2 SDS. Adan et al. [15] reported 9 cases who were treated with rhGH at a dose of 0.13 – 0.2 mg/kg/week. These patients lost 2.2 SDS over a 5.9-year treatment course, with the adult sitting height (-3.4 SDS) being even poorer than in our current study.

Xu et al. [40] analyzed 27 patients with CSRT and GH deficiency who were treated with rhGH at a dose of 0.3 mg/kg/week. Treatment was started (mean) 3.6 years after diagnosis, at an age of 11.3 years, with a mean duration of therapy of 6.1 years. Six patients received GnRH analogues for early puberty. Adult height was -1.9 SDS, with MPH at near zero SDS, these data being very similar to our current group. Height and sitting height achieved were inversely correlated with the age at diagnosis. In a subsequent report [12], these investigators contrasted patients who received conventional doses of CSRT (23–39 Gy) to those receiving 18 Gy. The latter group (of whom 7 of 10 survived) reached a mean adult height of -1.01 SDS in contrast to a group similar to their earlier

report, which achieved an adult height of -2.04 SDS. They affirmed the importance of the dosage of spinal irradiation in terms of adult height achievement in a group treated with about 50% more GH than our patients.

The group of medulloblastoma patients from KIGS, who were treated with rhGH to near adult height, is, to date, the largest group ($n = 113$) reported. We have expanded the analysis of patients treated within KIGS [16] by concurrently conducting a comparative study involving 1,986 patients with iGHD who were the same age at the start of therapy as the medulloblastoma group and had also reached near adult height (table 1). In children with iGHD, birth weight and MPH were significantly lower, while the degree of GH deficiency, the frequency of MPHD and the male to female ratio were very similar in both groups. At the start of GH therapy in which similar doses were applied, height and weight were less retarded in medulloblastoma, but sitting height was reduced. During the first year on GH there was a significantly higher increment in height in iGHD (8.2 vs. 7.9 cm/year; 0.5 vs. 0.4 Δ HT SDS). In prepubertal children treated during the first year, the 'index of responsiveness' [22] was significantly lower in medulloblastoma (-0.9 vs. -0.0 , $p < 0.001$). No major differences were observed between girls and boys. There were also no major differences between the groups who received or did not receive additional spinal irradiation.

Near-adult height was significantly lower in medulloblastoma. While patients with iGHD had grown into the normal range and had gained 1.6 SDS in height, the cohort with medulloblastoma had lost 0.3 SDS in height. TPG in the group of patients with reported onset of puberty was much lower in medulloblastoma as compared to iGHD (17.4 vs. 23.3 cm, $p < 0.01$). The 'index of responsiveness' was also much lower in medulloblastoma [25].

In the group with medulloblastoma followed to near height cessation, the multiple regression analysis shown above demonstrated that the near adult height correlated positively with age at the time the primary disorder was diagnosed (the older the child, the better). Likewise, final height correlated positively with the height at the start of

GH therapy. Among the patients in whom the disease onset began at under 5 years of age, in particular, a clear tendency towards less-than-normal height was observed. Significantly, 4 years elapsed between the primary diagnosis and the start of GH therapy, suggesting that the loss in height as the consequence of a delay in initiation of treatment could have impaired total height gain.

It must thus be concluded that the height gain through GH therapy (as applied in iGHD replacement dosages) in children with medulloblastoma is poor. Since this study involved data from the KIGS database, it was not possible to compare the results with an untreated cohort. It remains speculative, therefore, whether GH therapy may actually have prevented further loss in height. The reason for a poor response – compared to iGHD – is the impaired responsiveness to GH. The dosage of spinal irradiation that substantially influences vertebral growth appears to be of critical importance [12]. We assume that the GH dosages which are suitable for replacement in iGHD in KIGS, or even the higher dosages commonly prescribed in the USA will probably not lead to the achievement of height normalization in the case of medulloblastoma patients. It is possible that suitable dosages could be as high (or higher) than those applied in Turner syndrome or in small children following intrauterine growth retardation [41]. The caution regarding higher GH doses, with generation of higher IGF-I levels, in the setting of a post-cancer syndrome is obvious [42]. Since GHD is a likely consequence of the primary cancer therapy, efforts should be made to recognize impaired growth and GHD at an earlier point of time. Consequently, GH treatment could be introduced earlier and, in turn, greater height improvement could result. In order to ensure the safety of these measures, such treatment should necessarily be embedded in a complex, multidisciplinary and structured aftercare scheme. There are also promising, new primary treatment modalities being investigated, which show that postoperative chemotherapy alone may, in the future, possibly lead to a decrease in the degree of growth impairment in many of these children, and, in some cases, may prevent the occurrence of growth impairment [43].

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