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Elevated IGF-1 concentrations in children with low grade glioma: A descriptive analysis in a retrospective national cohort

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Abstract

Children with low grade glioma (LGG) may present with, or develop, elevated concentrations of insulin-like growth factor 1 (IGF-1). The prevalence, pathophysiology, or its possible clinical effects are poorly understood. Our aim was to evaluate the prevalence of such elevated IGF-1 concentrations and to describe its association with linear growth, body mass index (BMI), pituitary outcome, and tumor behavior in a large retrospective national cohort. From a nationwide retrospective cohort of pediatric brain tumor survivors diagnosed between 2002 and 2012, tumor, treatment, endocrine, and auxological data of children with LGG were collected ($n = 358$). Prevalence and risk factors for elevated IGF-1 concentrations, as well as the association between having elevated IGF-1 concentrations and receiving tumor treatment, were explored. IGF-1 concentrations had only been measured in 45.5% of cases ($n = 163/358$). In 18.4% of 163 children with available IGF-1 measurements, IGF-1 concentrations were found elevated. No association was described between having an elevated IGF-1 concentration and tumor behavior or height SDS at last moment of follow-up. Multivariate logistic regression identified posterior pituitary disorder (OR 6.14 95% CI: 2.21–17.09) and BMI SDS at follow-up (OR 1.56 95% CI: 1.09–2.20) to be significantly associated with elevated IGF-1 concentrations. In this retrospective cohort of children with LGG, IGF-1 was found elevated in 18.4% of children with available IGF-1 measurements. Elevated IGF-1 seems to be related to hypothalamic dysfunction worsening over time. Larger prospective cohort studies are needed.

KEYWORDS
hypothalamic dysfunction, insulin-like growth factor 1, low grade glioma

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1 | INTRODUCTION

Low grade glioma (LGG) are the most common pediatric brain tumor, accounting for approximately 30% of childhood brain tumors.[1] Although the survival rate has improved substantially (up to 85%–96%), treatment is challenging and survivors face many late effects of the tumor and/or its treatment, which may have a great impact on health and well-being in childhood.[2] Adverse effects include cognitive, visual, and neuroendocrine disorders.[3–6]

Children with suprasellar LGG have been described to present with or develop elevated insulin-like growth factor-1 (IGF-1) concentrations.[7,8] The etiology, prevalence and consequences of such elevated IGF-1 concentrations, such as on linear growth, energy metabolism or tumor growth, in children with LGG are, however, unknown. In addition, there is much debate about the role of IGF-1 on tumor growth, and the evidence for the relationship between IGF-1 and cancer in vivo, is contradictory.[9]

There have been different hypotheses on the etiology of elevated IGF-1 concentrations in LGG. First, a suprasellar tumor mass or increased pressure to the suprasellar area may disinhibit the hypothalamic–pituitary-GH-axis leading to (temporary) excessive GH secretion, with resultant increases in IGF-1 production. Second, IGF-1 concentration may be increased as consequence of circulating sex steroids (early puberty), increase in thyroid hormone, improvement of nutritional state, or as result of medication, such as glucocorticoids.[10,11]

The prevalence of patients with elevated IGF-1 concentrations is unclear, elevated concentrations of IGF-1 have been mainly described in infants with chiasmatic-hypothalamic tumors, who also present with diencephalic syndrome (DS).[12] DS is characterized by lack of appetite, impaired weight gain, or weight loss with loss of subcutaneous fat tissue despite normal caloric intake.[12,13] Having an elevated IGF-1 concentration in children with DS seems paradoxical because IGF-1 is known to decrease in a state of malnutrition and suggests GH hypersecretion to be present.[14]

Patients with prolonged elevated IGF-1 concentrations, such as patients with acromegaly, have been suggested to be at increased risk for cancer, especially colon carcinoma, although this association is still under debate.[15,16] Patients who lack or are resistant to IGF-1, such as patients with the Laron syndrome, are at decreased risk of cancer.[17,18] Research on this subject is scarce; a case–control study performed in adults on the association between IGF-1 and LGG, meningioma, and acoustic neuroma suggested a positive association between high concentrations of IGF-1 with LGG and acoustic neuroma, although reverse causation could not be excluded.[19] Next to worries about tumor growth, elevated IGF-1 concentrations may also affect linear growth. The influence of such high IGF-1 levels on final height in children with LGG is not known. Lastly, IGF-1 also has various metabolic effects and affects BMI.[20]

Because of the fact that many questions remain on the etiology and clinical effects of elevated IGF-1 concentrations in children with LGG, we aimed first to evaluate the prevalence of elevated IGF1 in children with LGG in a large national retrospective cohort. Subsequently, we aimed to describe its associations with linear growth, body mass index standard deviation score (BMI SDS), hypothalamic–pituitary outcome, and tumor behavior.

2 | METHODS

2.1 | Study population

Data was collected from a previous described nationwide retrospective cohort in the Netherlands.[21] This cohort consists of children (age < 18 years) diagnosed with a brain tumor (2002–2012) and survival >2 years ($n = 718$). In this nationwide cohort all endocrine data was collected (available in 98.6% survivors), with follow-up data until 2017. For the current study, only children with radiologically and/or histologically verified LGG were selected ($n = 358$).

2.2 | Data collection

Tumor- and treatment related characteristics, such as tumor location, tumor progression/relapse, tumor treatment (including number of relapse treatment), and state of disease were collected. In addition, data on anthropometric variables, and all available longitudinal endocrine laboratory measurements were collected from the database.

2.3 | Definitions

IGF-1 concentration was defined as elevated when the serum IGF-1 standard deviation score (IGF-1 SDS) was ≥+2, according to sex and age, in patients who did not receive treatment with GH. IGF-1 concentrations were calculated using assay specific references in each hospital and were not measured using a standardized protocol. IGF-1 concentrations measured during growth hormone replacement therapy were excluded. Underweight, overweight and obesity in infants (0–2 years) were defined as BMI SDS < −2.0, BMI SDS > 2.0 SDS, and BMI SDS > 3.0, respectively.[22] Underweight, overweight, and obesity for children aged ≥2 years were defined according to the international BMI cutoff points of Cole et al.[23,24]

Any pituitary disorder at follow-up was defined as having any disorder of the hypothalamic–pituitary system, including anterior pituitary hormone deficiencies (GH, thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), posterior pituitary dysfunction (diabetes insipidus [DI], and central precocious puberty [CPP]) found during follow-up (minimally 1 month after diagnosis). Follow-up time was defined as the time between moment of tumor diagnosis and last outpatient clinic visit as registered in the database.

2.4 | Statistical analysis

Data are presented as mean ± SD or median (range) for continuous data, depending on the distribution. Data are presented as

TABLE 1 Characteristics of children diagnosed with low grade glioma with and without available measurement of IGF-1.

Characteristics	All children with LGG ($n = 358$, 100%)	Children with IGF-1 measurements ($n = 163$, 45.5%)	Children without IGF-1 measurements ($n = 195$, 54.5%)	*p*-Value
Sex				
Male	181 (50.6)	75 (46.0)	106 (54.4)	0.116
Age at diagnosis, years	8.10 [0.10–17.60]	7.50 [0.20–17.0]	8.30 [0.10–16.8]	**0.010***
Age ≤ 2 years at diagnosis	41 (11.5)	27 (16.6)	14 (7.2)	**0.005***
Follow-up time, years	6.9 [2.0–13.4]	7.47 ± 3.24	6.44 ± 3.23	**0.003***
Neurofibromatosis type 1	31 (8.7)	14 (8.6)	17 (8.7)	0.966
Tumor location				**<0.001***
Infratentorial region	180 (50.3)	63 (38.7)	117 (60.0)	
Supratentorial region*	107 (29.9)	40 (24.5)	67 (34.4)	
Suprasellar region	71 (19.8)	60 (36.8)	11 (5.6)	
Hydrocephalus at diagnosis	202 (56.4)	94 (57.7)	108 (55.4)	0.664
Height SDS at diagnosis	0.04 ± 1.11	0.02 ± 1.14	0.07 ± 1.10	0.693
Height classification at diagnosis				
Between −2 and 2 SDS	314 (87.7)	149 (91.4)	165 (84.6)	0.764
Below −2 SDS	10 (2.8)	5 (3.1)	5 (2.6)	
Above 2 SDS	14 (3.9)	5 (3.1)	9 (4.6)	
Unknown	20 (5.6)	4 (2.5)	16 (8.2)	
Height SDS at follow-up	−0.23 ± 1.21	−0.43 ± 1.28	−0.04 ± 1.11	**0.004***
Height classification at follow-up				
Between −2 and 2 SDS	289 (80.7)	139 (85.3)	150 (76.9)	**0.008***
Below −2 SDS	20 (5.6)	16 (9.8)	4 (2.1)	
Above 2 SDS	15 (4.2)	5 (3.1)	10 (5.1)	
Unknown	34 (9.5)	3 (1.8)	31 (15.9)	
ΔHeight SDS	−0.22 [−4.08 to 4.35]	−0.33 [−4.08 to 4.35]	−0.18 [−2.73 to 2.81]	0.111
BMI SDS at diagnosis	0.44 ± 1.43	0.37 ± 1.55	0.51 ± 1.32	0.360
Weight classification at diagnosis				
Underweight	13 (3.6)	11 (6.7)	2 (1.0)	**0.026***
Normal weight	253 (70.7)	111 (68.0)	142 (72.8)	
Overweight	55 (15.4)	29 (17.8)	26 (13.3)	
Obesity	17 (4.7)	8 (4.9)	9 (4.6)	
Unknown	20 (5.6)	4 (2.5)	16 (8.2)	
BMI SDS at follow-up	0.97 ± 1.40	1.09 ± 1.39	0.86 ± 1.39	0.143
Weight classification at follow-up				
Underweight	2 (0.6)	2 (1.2)	0 (0.0)	0.181
Normal weight	218 (60.9)	101 (62.0)	117 (60.0)	
Overweight	73 (20.4)	42 (25.8)	31 (15.9)	
Obesity	30 (8.4)	15 (9.2)	15 (7.7)	
Unknown	35 (9.8)	3 (1.8)	32 (16.4)	
ΔBMI SDS	0.36 [−3.15 to 8.36]	0.57 [−3.15 to 8.36]	0.24 [−2.83 to 4.52]	0.088
Pituitary disorder at follow-up	30 (8.4)	30 (18.4)	0 (0.0)	**<0.001***
Central precocious puberty	29 (8.1)	28 (17.2)	1 (0.5)	**<0.001***
Treatment				
Wait and see	2 (0.6)	1 (0.6)	1 (0.5)	**<0.001***
Surgery only	272 (76.0)	89 (54.6)	183 (93.8)	
Surgery + CT	37 (10.3)	29 (17.8)	8 (4.1)	

(Continues)

TABLE 1 (Continued)

Characteristics	All children with LGG ($n = 358$, 100%)	Children with IGF-1 measurements ($n = 163$, 45.5%)	Children without IGF-1 measurements ($n = 195$, 54.5%)	*p*-Value
Surgery + RT	34 (9.5)	31 (19.0)	3 (1.5)	
Surgery + CT + RT	13 (3.6)	13 (8.0)	0 (0.0)	
Chemotherapy	51 (14.2)	42 (25.8)	9 (4.6)	**<0.001***
Radiotherapy	47 (13.1)	44 (27.0)	3 (1.5)	**<0.001***
Tumor progression at follow-up	85 (23.7)	64 (39.3)	21 (10.8)	**<0.001***
State of disease at follow-up				
Complete remission	175 (48.9)	50 (30.7)	125 (64.1)	**<0.001***
Residual disease	183 (51.1)	113 (69.3)	70 (35.9)	

Note: Numbers are presented as *n* (%), mean ± SDS, or median [range]. Between-group differences were evaluated by student's *t* test for continuous data with a normal distribution, Mann–Whitney U test for continuous data with a skewed distribution, and by χ2 test or Fisher's exact test for categorical data.
Abbreviations: BMI, body mass index; CT, chemotherapy; RT, radiotherapy; SDS, standard deviation score.
*Supratentorial region without suprasellar area (e.g., cerebral hemispheres, tectum, thalamus).

percentages for categorical variables. Between-group differences were evaluated by Student's *t* test for continuous data with a normal distribution, Mann–Whitney U test for continuous data with a skewed distribution, and by χ^2 test or Fisher's exact test for categorical data. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro–Wilk's test were employed. Differences in patient characteristics and tumor response at diagnosis and follow-up were compared between children with or without elevated IGF-1 concentrations. Independent variables to be included in the univariate logistic regression were selected by considering the clinical relevance of each variable. IGF-1 measurements were plotted against tumor treatment to explore possible association. A *p*-value of < .05 was considered statistically significant. Analyses were performed using SPSS version 26.0.

3 | RESULTS

3.1 | Study population

Of the 358 patients with LGG, in 45.5% IGF-1 measurements were available ($n = 163$). Characteristics of children with and without available IGF-1 measurements are listed in Table 1. Age at diagnosis, follow-up time, suprasellar tumor location, small height SDS at follow-up (≤−2 SDS), underweight at diagnosis, presence of pituitary disorders at any time, multiple treatment modalities, and tumor progression or residual disease at follow-up, were significantly associated with the availability of IGF-1 measurements ($p < .05$). Of all patients with measurements ($n = 163$), in 96 patients (58.9%) IGF-1 had been measured at diagnosis and in 141 (86.5%) IGF-1 was measured during follow-up, and in 74 (45.3%) both at diagnosis and during follow-up. Median number of IGF-1 measurements per patient were 4 [1–31].

Of the 163 included patients, LGG was located infratentorial in 38.7%, supratentorial non-suprasellar in 24.5%, and suprasellar in 36.8%, respectively. The most prevalent histological diagnosis was pilocytic astrocytoma (76.7%), diffuse astrocytoma (8.0%), and gangliolioma (7.4%). Median age at tumor diagnosis was 7.50 years [0.20–17.00] and median follow-up time was 7.14 years [0.50–15.00]. In total, 162/163 (99.4%) had been treated with neurosurgery, 42/163 (25.8%) with chemotherapy, and 44/163 (27.0%) with radiotherapy. At the end of follow-up, 50/163 (30.7%) were in complete remission and 113/163 (69.3%) had stable residual disease.

3.2 | Percentage of patients with elevated IGF-1 concentrations

In 30/163 (18.4%) children, one or more elevated IGF-1 (≥+2 SDS) concentrations were found. In 16 children, elevated IGF-1 concentrations were found within 3 months of diagnosis, and in 14 children at any time point during follow up. Median time between diagnosis and first measurement of elevated IGF-1 concentration was 3.50 months [0.00–111.00]; median age at time of first measurement of elevated IGF-1 concentration was 6.80 years [0.80–17.40]. In total, there were 202 IGF-1 measurements available in these 30 children, with a median value of 1.47 SDS [−4.30 to 5.46]. Of these, 81 (40.0%) measurements were elevated, with a median of +2.62 SDS [2.00–5.46]. The median number of measurements per patient was 5 [1–25]. Of all IGF-1 measurements, none of the subjects had received GH therapy prior to IGF-1 measurement. None had been treated with somatostatin analogues.

3.3 | Patient characteristics associated with elevated IGF-1 concentrations

Of 30 children with elevated IGF-1 concentrations, 16 (53.3%) were male and 14 (46.7%) were female. Median age at diagnosis was 5.20 years [0.60–15.00], of whom eight children (29.6%) were aged ≤2 years at time of diagnosis (Table 2). The most common tumor location was the suprasellar region (63.3%). None of the tumors were located in the supratentorial region (e.g., cerebral hemispheres,

TABLE 2 Characteristics of children diagnosed with low grade glioma with and without IGF-1 elevation.

Characteristics	IGF-1 elevation ($n = 30$, 18.4%)	No IGF-1 elevation ($n = 133$, 81.6%)	p-value
Sex			
Male	16 (53.3)	59 (44.4)	.373
Age at diagnosis, years	5.18 [0.56–15.01]	8.21 [0.21–16.98]	**.033***
Age ≤2 years at diagnosis	8 (26.7)	19 (14.3)	.109
Follow – up time, years	7.17 [0.90–15.00]	7.14 [0.50–14.90]	.563
Neurofibromatosis type 1	6 (20.0)	8 (6.0)	**.024***
Tumor location			
Infratentorial region	11 (36.7)	52 (39.1)	**.001***
Supratentorial region**	0 (0.0)	40 (30.1)	
Suprasellar region	19 (63.3)	41 (30.8)	
Height SDS at diagnosis	0.59 ± 1.27	−0.10 ± 1.08	**.008***
Height classification at diagnosis			
Between −2 and 2	25 (83.3)	124 (93.2)	**0.009***
Below −2	0 (0.0)	5 (3.8)	
Above 2	4 (13.3)	1 (0.8)	
Unknown	1 (3.3)	3 (2.3)	
Height SDS at follow-up	−0.29 ± 1.38	−0.43 ± 1.25	0.482
Height classification at follow-up			
Between −2 and 2	22 (73.3)	117 (88.0)	.181
Below −2	4 (13.3)	12 (9.0)	
Above 2	2 (6.7)	3 (2.3)	
Unknown	2 (6.7)	1 (0.8)	
BMI SDS at diagnosis	0.36 ± 2.26	0.37 ± 1.35	.994
Weight classification at diagnosis			
Normal	14 (46.7)	97 (72.9)	**.003***
Underweight	4 (13.3)	7 (5.3)	
Overweight	6 (20.0)	23 (17.3)	
Obesity	5 (16.7)	3 (2.3)	
Unknown	1 (3.3)	3 (2.3)	
BMI SDS at follow-up	1.96 ± 1.24	0.90 ± 1.36	**<.001***
Weight classification at follow-up			
Normal	8 (26.7)	93 (69.9)	**<.001***
Underweight	1 (3.3)	1 (0.8)	
Overweight	12 (40.0)	30 (22.6)	
Obesity	7 (23.3)	8 (6.0)	
Unknown	2 (6.7)	1 (0.8)	
Treatment			
Wait and see	0 (0.0)	1 (0.8)	.074
Surgery only	16 (53.3)	73 (54.9)	
Surgery + CT	10 (33.3)	19 (14.3)	
Surgery + RT	2 (6.7)	29 (21.8)	
Surgery + CT + RT	2 (6.7)	11 (8.3)	
Tumor progression requiring treatment	14 (46.7)	51 (38.3)	.194
Number of relapse treatment			
1	11 (78.6)	36 (70.5)	.298
2	1 (7.1)	8 (15.7)	
3	1 (7.1)	7 (13.7)	
4	1 (7.1)	0 (0.0)	
State of disease at last moment of follow-up			
Complete remission	7 (23.3)	43 (32.3)	.334
Residual disease	23 (76.7)	90 (67.7)	

Note: Numbers are presented as *n* (%), mean ± SDS, or median [range]. Between-group differences were evaluated by student's *t* test for continuous data with a normal distribution, Mann–Whitney U test for continuous data with a skewed distribution, and by χ^2 test or Fisher's exact test for categorical data.

Abbreviations: BMI, body mass index; CT, chemotherapy; RT, radiotherapy; SDS, standard deviation score.

*Statistically significant.

**Supratentorial region without suprasellar area (e.g., cerebral hemispheres, tectum, thalamus).

tectum, and thalamus). The most prevalent histological diagnosis in the 30 children with elevated IGF-1 concentration was pilocytic astrocytoma (90.0%). Ten of 11 children (90.1%) with elevated IGF-1 concentration and an infratentorial tumor had concurrent hydrocephalus at diagnosis. In 6/30 (20.0%) children, neurofibromatosis type I (NF-1) was diagnosed and all had a suprasellar LGG. Underweight at diagnosis was present in four (13.3%) children, 14 (46.7%) were normal weight, six (20.0%) were overweight, five (16.7%) were obese, and of one BMI at diagnosis was unknown.

In our cohort, eight children (29.6%) were aged ≤2 years at time of diagnosis. Of these eight children, six children were diagnosed with a suprasellar LGG and presented with a clinical picture of diencephalic syndrome at moment of diagnosis. Median BMI SDS at diagnosis was −2.03 [−1.64 to −4.79] and median BMI SDS at follow-up was 2.44 [0.14–4.25], after a median follow-up time of 6.94 years. Three children had elevated IGF-1 concentrations at moment of diagnosis, the other three at 7, 11, and 19 months after diagnosis, respectively.

Elevated IGF-1 concentration was univariate associated with suprasellar tumor location, age at diagnosis, neurofibromatosis type I, underweight or obesity at diagnosis, height SDS corrected for target height SDS, posterior pituitary disorder, and BMI SDS at follow-up. Multivariate

logistic regression identified posterior pituitary disorder during follow-up (OR 6.14 95% CI: 2.21–17.09) and increased BMI SDS at follow-up (OR 1.56 95% CI: 1.09–2.23) as statistically significant (Table 3).

3.4 | Linear growth and BMI

In the children with elevated IGF-1 concentrations, mean height SDS at diagnosis was 0.59 ± 1.27 and mean height SDS at follow-up was −0.29 ± 1.38. Height SDS corrected for target height SDS at diagnosis was significantly associated with elevated IGF-1 concentration, but height SDS corrected for target height SDS at follow-up was not.

Children with an elevated IGF-1 concentration were significantly at risk to develop overweight or obesity at follow-up ($p < .001$). In children with an elevated IGF-1 concentration, 12/30 (40.0%) developed overweight and 7/30 (23.3%) obesity at follow-up, compared to 30/133 (22.6%) and 8/133 (6.0%), of children with a normal IGF-1 concentration. All four children (100%) with an elevated IGF-1 concentration and underweight at diagnosis developed overweight or obesity at last moment of follow-up. In the children without elevated IGF-1 concentration, seven children (5.3%) were underweight at diagnosis, of whom 3/7 (42.9%) developed overweight.

3.5 | Tumor behavior in relation to IGF-1 concentrations

The majority of children with elevated IGF-1 concentrations had residual disease at last moment of follow-up ($n = 23/30$, 76.7%). Seven children (23.3%) were in complete remission at last moment of follow-up, all of whom had an infratentorial tumor and had received surgery only. Of the children with an elevated IGF-1 concentration, 14/30 (46.7%) had tumor progression requiring treatment during follow-up, compared to 51/133 (38.3%) without elevated IGF-1 concentration. No association was found between an elevated IGF-1 concentration and tumor progression ($p = .402$).

In 16/30 children (53.3%) with elevated IGF-1 concentrations, IGF-1 concentration had been measured ≥ five times at various time points. In 8/16 (50.0%) children, variations in IGF-1 concentrations were observed over time, in which IGF-1 concentrations alternately decreased and increased to values within (−2 SDS up to +2SDS) and above the reference range. In six children, this was during or between chemotherapy courses (Figure 1A, ID 1, 5, 8, 9, 10, 13) and in two children (Figure 1A, ID 3 and 6) this was after tumor treatment. In 8/16 children (50.0%), no fluctuations were seen. Of these 16 children with multiple IGF-1 measurements, one or more relapses during follow-up occurred in 11 (68.8%) children. In 6/8 (75.0%) children with IGF-1 fluctuations, one or more tumor relapses were observed compared to 5/8 (62.5%) children without IGF-1 fluctuations ($p = 0.99$). Differences in characteristics between patients with fluctuations ($n = 8$) versus patients without fluctuations ($n = 8$) were age at diagnosis (median 1.71 years [0.59–15.01] vs. 5.73 years [0.56–12.04]), height SDS at diagnosis (−0.15 SDS [−1.34–3.53] vs. 0.68 [0.01–2.60]), and pituitary disorders at follow-up (87.5% vs. 62.5%) (all p = NS). Figures 1 and 2 shows a detailed overview of tumor treatment in relation to IGF-1 measurements.

3.6 | IGF-1 after LGG treatment

In 15/30 (50.0%) children with elevated IGF-1 concentration, IGF-1 concentration had been measured both during and after LGG treatment. In 7/15 children (46.7%) elevated IGF-1 concentration emerged or persisted

TABLE 3 Univariate and multivariate logistic regression of elevated IGF-1 concentrations.

	Univariate analysis					Multivariate analysis				
		95% confidence interval					95% confidence interval			
	Odds ratio	Lower		Upper	*p*-value	Odds ratio	Lower		Upper	*p*-value
Suprasellar location[a]	3.88	1.69	–	8.88	.001*					
Age at diagnosis (years)	0.90	0.82	–	0.99	.031*					
Neurofibromatosis type 1	3.91	1.24	–	12.28	.020*					
Underweight at diagnosis	3.96	1.03	–	15.28	.046*					
Obesity at diagnosis	8.82	1.98	–	39.38	.004					
Height SDS[b] at diagnosis	1.72	1.09	–	2.71	.019*					
BMI SDS at follow-up	1.81	1.30	–	2.53	<.001*	1.56	1.09	–	2.23	.015*
Anterior pituitary deficiency at follow-up	1.85	0.60	–	5.65	.282	0.89	0.24	–	3.30	.889
Posterior pituitary deficiency (DI/CPP) at follow-up	6.42	2.12	–	18.41	<.001*	6.14	2.21	–	17.09	<.001*

Note: Univariable and multivariable logistic regression for risk factors of patients with LGG and elevated IGF-1 concentrations ($n = 30$) compared to LGG patients without elevated IGF-1 concentrations ($n = 133$).

Abbreviations: BMI SDS, body mass index standard deviation score; CCP, central precocious puberty; DI, diabetes insipidus.

*Statistically significant.

[a]Suprasellar brain tumors versus other brain tumors.

[b]Corrected for target height SDS.

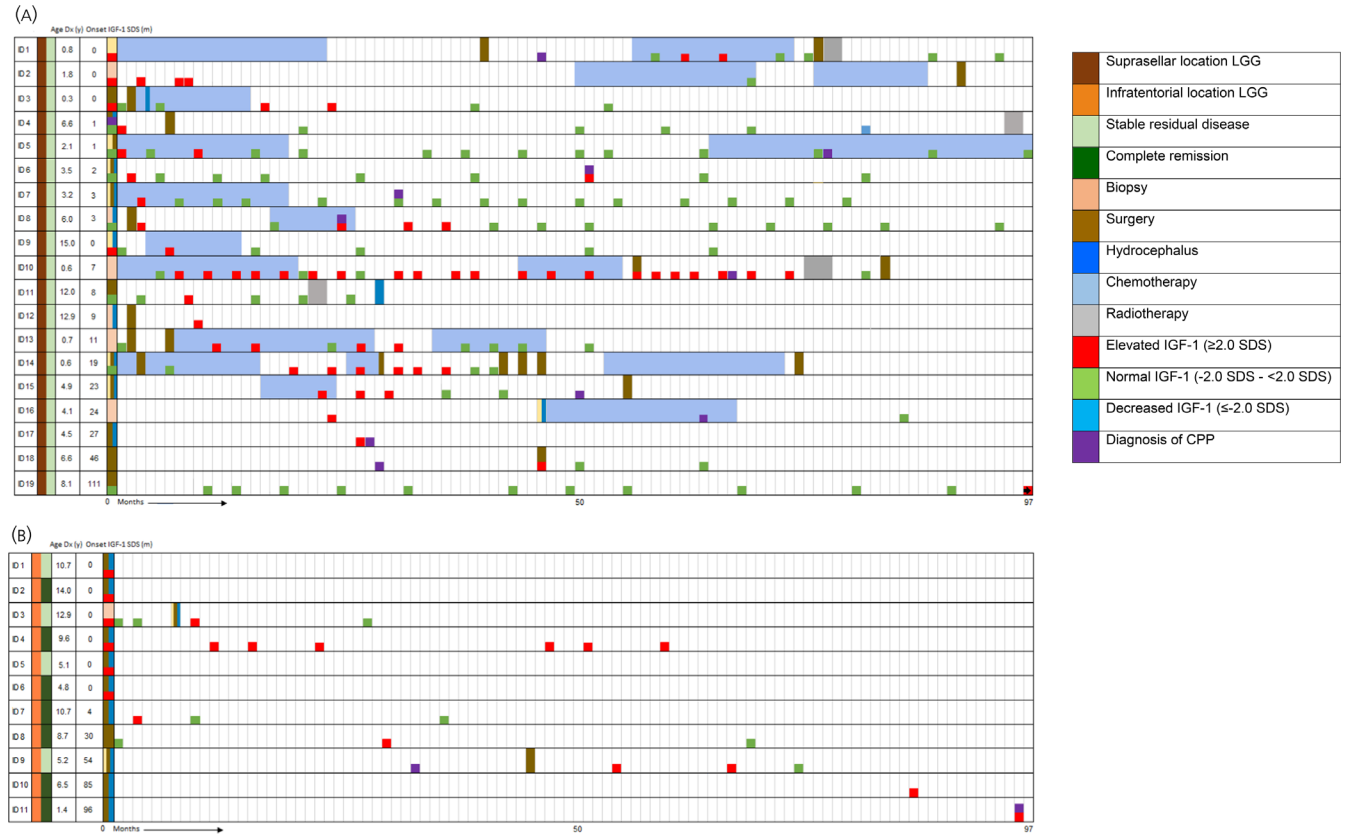

FIGURE 1 Detailed overview of IGF-1 measurements and low grade glioma (LGG) treatment. (A) Suprasellar LGG. (B) Infratentorial LGG. Dx, diagnosis; IGF-1, insulin-like growth factor 1; m, month; SDS, standard deviation score; y, years. *One square represents 1 month from moment of diagnosis on.

after LGG treatment, in 7/15 (46.7%) IGF-1 concentration normalized (IGF-1 between −2 and +2 SDS), and in 1/15 (6.7%) IGF-1 concentration decreased to <−2 SDS and GH deficiency was found. In 7/30 (23.3%) children, IGF-1 concentration had only been measured during LGG treatment and in 8/30 (26.7%) children, IGF-1 concentration had only been measured after completing LGG treatment. In a total of 15/23 (65.2%) children, elevated IGF-1 concentrations were found after completing LGG treatment. Of these, 5/15 (33.3%) children (Figure 1B, ID 4, 7, 8, 10, and 11) had elevated IGF-1 concentrations, while no residual tumor was present (these children achieved complete remission).

3.7 | Pituitary disorders during follow-up

In 14 of 30 children (46.7%) with elevated IGF-1 concentration, one or more pituitary disorders had been diagnosed during follow-up compared to 16 of 133 children (12.0%) without elevated IGF-1 concentration ($p < .001$). Percentage of anterior pituitary deficiencies at follow-up were not statistically different between children with elevated IGF-1 concentrations and children without (10.0% vs. 3.8%, $p = .164$). Posterior pituitary deficiencies at follow-up were statistically significantly different, CPP was present in 43.3% versus 9.0% ($p < .001$) and DI in 10.0% versus 1.5% ($p = .044$). In 7/13 (53.8%) children elevated IGF-1 concentration and CPP were present at the same time, of whom four already had elevated IGF-1 concentrations before CPP occurred and in three IGF-1 was elevated during diagnosis of CPP. CPP at follow-up was observed in 3/6 (50.0%) children with NF-1 and elevated IGF-1 concentration, and in 10/24 (41.7%) children without NF-1 and elevated IGF-1 concentration.

4 | DISCUSSION

With the data collected in this retrospective nationwide pediatric brain tumor cohort, we have tried to give a more detailed description of prevalence and associations of elevated IGF-1 in childhood LGG. We found that IGF-1 concentrations were measured in only 45.5% of children. Of the children in which IGF-1 was measured, IGF-1 was elevated in 18.4%. Occurrence of IGF-1 elevations seems to be related, but not limited to suprasellar location of the tumor and younger age at diagnosis. Children with LGG and an elevated IGF-1 concentration seem to be at a higher risk to develop higher BMI SDS and posterior pituitary dysfunction at follow-up. We could not detect an association between tumor behavior and IGF-1 elevations, but our conclusions should be considered with caution due to the very low number of patients and events.

The fact that children with an elevated IGF-1 concentration were significantly at risk to develop overweight or obesity at follow-up may reflect hypothalamic dysfunction increasing in time. Hypothalamic obesity is a result of a disbalance of the anorexic neurons (leptin and

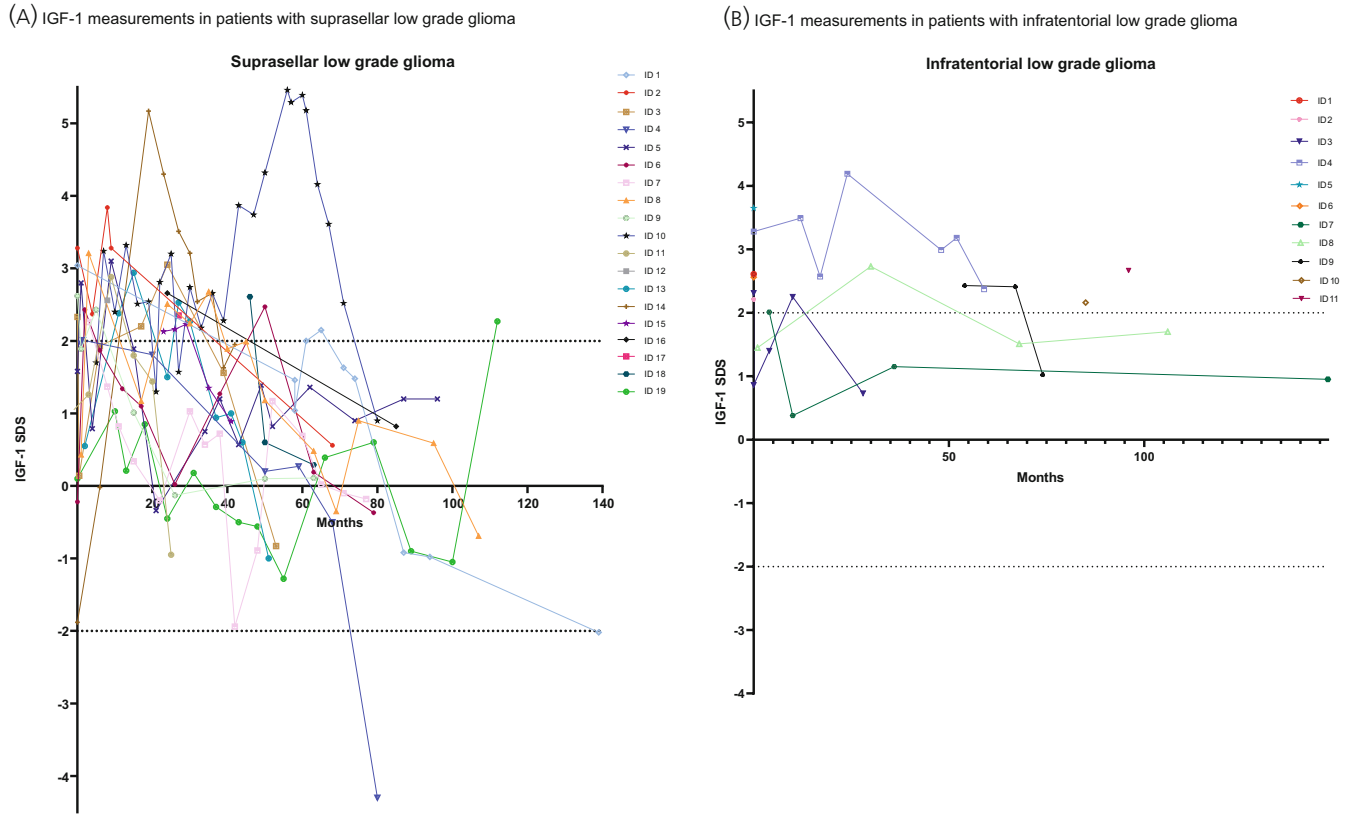

FIGURE 2 Plot of IGF-1 measurements. (A) IGF-1 measurements in patients with suprasellar low grade glioma (LGG). (B) IGF-1 measurements in patients with infratentorial LGG.

insulin sensitive neurons) and orexigenic neurons (ghrelin sensitive neurons).[25] Orexigenesis with defective hypothalamic – leptin signaling leads to increased appetite, increased energy storage, and decreased energy expenditure with consequently the development of hypothalamic obesity.[26] The mechanism of diencephalic syndrome in children with LGG is poorly understood. The switch phenomenon of these children, presenting with underweight but developing obesity during follow-up may be the consequence of changing phenotype due to maturation of the hypothalamus.[15,24,25] In our cohort, we also found children with DS developing overweight or obesity at follow-up. The elevated IGF-1 in these children may also be considered to be caused by hypothalamic dysfunction (imbalance of stimulating and inhibiting factors) which changes in time, due to maturation of the hypothalamus with spontaneous normalization of IGF-1 in due time and even progression into GH deficiency in some.

In the general population, nutritional state is known to influence the IGF-1 concentration. Anorexia leads to decreased nutritional intake and lower BMI and lower IGF-1 concentrations.[27] In this light, an elevated IGF-1 concentration in children with DS seems paradoxical. It has been suggested that the elevated IGF-1 concentrations in children with DS is a reflection of hypothalamic dysfunction resulting in GH hypersecretion.[7,12,13] GH stimulates lipolysis and regulates lipid deposition, mostly via IGF-1, and excessive GH release may cause weight loss and underweight. Children with DS have also been described to have normal IGF-1 concentrations, and it remains an interesting puzzle why some children with DS have elevated IGF-1 concentrations and others do not.[28] The anorectic clinical picture of children with DS may be the result of hypothalamic damage (damage of the orexin-producing hypothalamic neurons) or it may even be hypothesized that the lack of appetite and undernutrition observed in children with DS is a protective brain response to prevent further rise of IGF-1 concentration (as increasing BMI may increase/normalize the IGF-1 concentrations) and thus prevent possible cell proliferation and tumor growth.[7,10] In DNA-repair deficient mice, diet restriction has shown to extend lifespan by suppressing growth and enhance cellular maintenance.[29]

Whether elevated IGF-1 affects tumor behavior remains a matter of debate. In the univariate analysis elevated IGF-1 concentration and tumor relapse were not associated. In addition, by creating a timeline of events (Figure 1), we could not detect a trend between elevated IGF-1 concentrations and tumor behavior, defined as tumor relapse. The lack of association between an elevated IGF-1 concentration and tumor relapse is particularly reassuring; however, it should be borne in mind that IGF-1 measurements (and therefore the likelihood of an elevated concentration) are more likely in progressive tumors, as illustrated in Table 1. Although our data concerns the largest cohort thus far described the retrospective nature and the low number of events in our study has too many limitations, making it impossible to draw solid conclusions. We recommend future prospective trials with

systematic measurements of IGF-1 in all children with LGG from the moment of diagnosis to the last moment of follow-up.

In contrast to our expectations, our cohort showed that not only children with a suprasellar tumor, but also children with an infratentorial tumor could develop an elevated IGF-1 concentration. Almost all children with an infratentorial tumor and elevated IGF-1 concentration presented with hydrocephalus at diagnosis, for this reason it may be considered that the elevated IGF-1 concentration is due to increased pressure on the HP-axis. Future research should explore the role between hydrocephalus and elevated IGF-1 concentrations.

In the 30 children, we found no effect of having had an elevated IGF-1 concentration on height SDS at last moment of follow-up. It should be taken into account, however, that many factors influence height in children with LGG such as nutrition, endocrine, ill-being due to chemotherapy or the tumor itself. Regarding other endocrine factors influencing height, CPP was present in 43.3% and GHD in 3.3%, respectively. Unfortunately, bone age was not available for all patients and thus could not be taken into account in the interpretation of linear growth or IGF-1 SDS. For this reason, to draw a conclusion on IGF-1 and height SDS at follow-up must be taken cautiously.

The current study is the first more detailed description elevated IGF-1 concentrations in childhood LGG, reporting the prevalence and its associations. Considering the retrospective and non-systematic nature of this report and low patient numbers, the results presented here are purely descriptive. The true prevalence of IGF-1 elevation may be over or underestimated. We aimed to provide researchers and clinicians more insight upon the phenomenon of elevated IGF-1 concentration in children with LGG. Our results illustrate the need for future prospective studies to give more insight into the pathophysiology and clinical relevance of elevated IGF-1 concentrations.

In conclusion, in this nationwide cohort, we found elevated IGF-1 concentrations to be present in 18.4% of the tested children. To our surprise, not only children with suprasellar LGG presented with or developed elevated IGF-1 concentrations. Children with elevated IGF-1 concentrations seem to be at increased risk for (hypothalamic) overweight and posterior pituitary disorder during follow-up. Future prospective studies are needed with standardized measurements of IGF-1 concentration at time of diagnosis, during treatment and during follow-up to better understand its etiology and its possible association with tumor behavior.

AUTHOR CONTRIBUTIONS

Jiska van Schaik: Formal analysis; methodology; visualization; writing – original draft; writing – review and editing. **Ichelle van Roessel:** Formal analysis; methodology; visualization; writing – original draft; writing – review and editing. **Iris Bos:** Formal analysis; writing – original draft; writing – review and editing. **Hedi Claashen-van der Grinten:** Resources; writing – review and editing. **Sarah Clement:** Data curation; project administration; writing – review and editing. **Laura van Iersel:** Data curation; investigation; methodology; project administration; writing – review and editing. **Boudewijn Bakker:** Resources; writing – review and editing. **Lisethe Meijer:** Resources; writing – review and editing. **Leontien Kremer:** Funding acquisition; investigation; methodology; resources; writing – review and editing. **Netteke Schouten-van Meeteren:** Data curation; funding acquisition; methodology; resources; supervision; validation; writing – review and editing. **Hanneke van Santen:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

ETHICS STATEMENT

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Because data were collected retrospectively, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver.

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