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RESEARCH

Bone health in childhood low-grade glioma: an understudied problem

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Abstract

Objective: Children with a supratentorial midline low-grade glioma (LGG) may be at risk for impaired bone health due to hypothalamic-pituitary dysfunction, obesity, exposure to multiple treatment modalities, and/or decreased mobility. The presence of impaired bone health and/or its severity in this population has been understudied. We aimed to identify the prevalence and risk factors for bone problems in children with supratentorial midline LGG.

Materials and methods: A retrospective study was performed in children with supratentorial midline (suprasellar or thalamic) LGG between 1 January 2003 and 1 January 2022, visiting the Princess Máxima Center for Pediatric Oncology. Impaired bone health was defined as the presence of vertebral fractures and/or very low bone mineral density (BMD).

Results: In total, 161 children were included, with a median age at tumor diagnosis of 4.7 years (range: 0.1–17.9) and a median follow-up of 6.1 years (range: 0.1–19.9). Five patients (3.1%) had vertebral fractures. In 99 patients, BMD was assessed either by Dual Energy X-ray Absorptiometry ($n = 12$) or Bone Health Index ($n = 95$); 34 patients (34.3%) had a low BMD (≤ −2.0). Impaired visual capacity was associated with bone problems in multivariable analysis (OR: 6.63, 95% CI: 1.83–24.00, $P = 0.004$).

Conclusion: In this retrospective evaluation, decreased BMD was prevalent in 34.3% of children with supratentorial midline LGG. For the risk of developing bone problems, visual capacity seems highly relevant. Surveillance of bone health must be an aspect of awareness in the care and follow-up of children with a supratentorial midline LGG.

Significance statement

Patients with supratentorial midline LGG may encounter various risk factors for impaired bone health. Bone problems in survivors of childhood supratentorial midline LGG are, however, understudied. This is the first paper to address the prevalence of bone problems in this specific patient population, revealing visual problems as an important risk factor. Diencephalic syndrome historyand/or weight problems associated with hypothalamic dysfunction were related to bone problems in univariate analyses. The results of this study can be used in the development of guidelines

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to adequately screen and treat these patients to subsequently minimizing bone problems as one of the endocrine complications.

Keywords: bone surveillance; childhood cancer survivors; hypothalamic-pituitary dysfunction; overweight; suprasellar; visual problems

Introduction

Endocrine complications are common in up to 60% of childhood cancer survivors (CCS) (1). Deprived bone health, ranging from low bone mineral density (BMD) to bone pain and fractures, is a prevalent late effect, and brain tumor survivors especially have a higher risk of fractures and low BMD (2, 3). Multiple risk factors for impaired bone health in CCS have been described (4, 5, 6, 7, 8, 9, 10).

Low-grade glioma (LGG) is the most frequent brain tumor in children (11) with a survival rate of more than 90% after multimodal treatment (12). The adverse effects of the tumor and treatment may severely impact quality of life (13). Children with suprasellar LGG may develop hypothalamic-pituitary dysfunction (HD), resulting in pituitary insufficiency, decreased energy expenditure, overweight and obesity, disturbed day–night rhythm, loss of initiative, hyperphagia, and behavioral problems (14). Overweight and obesity are well-known risk factors for impaired bone mineralization (15, 16). Besides the increase in body mass index (BMI), pituitary deficiencies and immobilization (due to visual problems, fatigue, and/or lack of initiative) are common in these patients and may contribute to bone problems (17). Lastly, children with progressive LGG are often exposed to multiple chemotherapy treatments and new targeted therapies such as inhibitors of the RAS/MAPK signaling pathway, which may negatively influence bone health (18, 19, 20).

Negative disruption of the balance between bone formation and bone resorption is a process that may occur gradually and during disease without initially causing pain or other symptoms. Often, deprived bone health is not noticed until a fracture occurs. Bone mineral density (BMD), as a marker of bone health, can be determined by dual-energy x-ray absorptiometry (DXA) (21). BMD is also reflected by the bone health index (BHI), obtained by measuring metacarpal cortical thickness on x-ray using BoneXpert image analyzing software (22, 23). BMD is an indicator of the bone mineral content of bones.

Even though children with supratentorial midline LGG have multiple risk factors for bone problems, its prevalence or severity has to our knowledge not been described. Awareness of impaired bone health and its associated factors, however, would open doors towards surveillance and prevention, such as combined lifestyle programs and early start of vitamin D, calcium, and/or pituitary hormone substitution.

The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) recommends screening of bone problems in all CCS treated with cranial radiotherapy (2). For children with LGG, rarely treated with radiotherapy, there is no surveillance protocol for bone health. The aim of this study is to give a detailed description of the prevalence and severity of bone problems and impaired bone health in children with supratentorial midline LGG and to describe its associated factors.

Materials and methods

Study design and population

The Dutch supratentorial midline LGG cohort in collaboration with the 'Dutch Childhood Oncology Group registry', was used for selection of patients (https://www.skion.nl/). Patients that had all visited the national center for pediatric oncology, the Princess Máxima Center, Utrecht, The Netherlands, between the opening of the center (2018) and 2022 were selected.

Inclusion criteria were: supratentorial midline LGG (suprasellar or thalamic origin), diagnosed between 1 January 2003 until 1 January 2022 ($n = 161$), aged ≤18 years at time of tumor diagnosis, and minimum follow-up time of 1 year. Thalamic tumors with involvement of the suprasellar area were included. Patients with an optic nerve glioma without involvement of the optic chiasm were excluded.

Data collection

Data were retrospectively collected from medical records.

Operational definitions

Outcomes

'Any' bone problems were defined as the single occurrence or combinations of the following situations: vertebral fractures grade I-III according to the Genant semiquantitative method (on MRI scan or x-ray of the spine) (9, 24), 'very low BMD' on a DXA scan (21), or 'very low BMD' as determined by BHI (22). The presence of a bone problem was assessed as a binary outcome and a patient with multiple bone problems was only scored once.

'Very low BMD' was defined as a *Z*-score of ≤ −2.0 on the DXA scan (21) or a BHI of ≤ −2.0 SDS, corrected for sex and biological age (25). BMD *Z*-scores from the total body less head from DXA were used and adjusted for height at time of measurement (26). BHI was assessed by digital x-ray radiogrammetry of the hand (22, 23). If both DXA and BHI were assessed at the same time (maximum 3 months apart), without other bone problems, the DXA values were decisive.

'At risk for low BMD' was defined as a *Z*-score on the DXA scan between −1.0 and −2.0 or a BHI between −1.0 and −2.0 SDS, corrected for sex and age (reference population: healthy Dutch children) (27). Prevalence of bone problems could only be described in the children in whom bone assessment was done. As part of the sensitivity analysis, all analyses were repeated in all children with supratentorial midline LGG. For this sensitivity analysis, if information on bone assessment was missing it was assumed that there were no (clinically relevant) bone problems.

Pituitary dysfunction was defined as having any anterior pituitary deficiency, posterior pituitary deficiency, or central precocious puberty (CPP) (Supplementary 1 and 2, see section on supplementary materials given at the end of this article).

Hypothalamic dysfunction was defined according to the diagnostic criteria for hypothalamic syndrome (HS) (17).

Associated factors with bone health

Factors were assessed throughout follow-up until the occurrence of bone health complications (Supplementary 1). The last moment of follow-up was defined as the first occurrence of the bone problem for children with a bone problem, or the last hospital visit (outpatient or inpatient) for children without a bone problem.

Statistical analyses

For normally distributed variables, the mean value was calculated with SD. For non-normally distributed data, the median value was calculated with the full range and interquartile range (IQR). Characteristics were compared between groups with and without bone problems. The Pearson chi-squared test was used for the association between categorical data (and Fisher's exact for more than 20% of expected values under five). For analyses of continuous variables with a non-normal distribution, the Mann–Whitney *U* test was performed and for a normal distribution the Student's *t*-test. Assessment of normality of the variables was done using a QQ plot and the Shapiro–Wilk test.

The compound outcome 'any bone problems' was assessed in binary multivariable logistic regression. Covariates found to be significant in univariate analyses and/or clinically relevant were included in the multivariable model. The maximum number of covariates included was based on the number of patients in which the outcome was present (one covariate for every ten patients). The Wald test was used to calculate the *P*-values. *P*-values <0.05 were considered significant. All analyses were performed by using SPSS version 29.0 (IBM, USA) and R version 4.3.0 (R core team, Vienna, Austria) (packages; haven, dplyr, tidyr, tibble, tidyverse, ggplot2).

Ethics

All patients and parents had given written informed consent for the use of medical data. The Dutch IRB METC NedMec, Utrecht, decided that no additional procedures were required.

Results

Study population

In total, 161 patients with a supratentorial midline LGG were included in this study (Supplementary Table 1). Of them, 49.1% (79/161) were female and the median age at diagnosis of the supratentorial midline LGG was 4.7 years (range: 0.1–17.9). Of all patients, 75.0% (111/148) had experienced one or more tumor progressions during follow-up. In total 55.3% (89/161) had been treated with neurosurgery, 70.2% (113/161) with chemotherapy, 27.3% (44/161) with targeted therapy, and 8.1% (13/161) with radiotherapy. At the time of tumor diagnosis 60.9% (70/115) of patients had a normal weight, 16.5% (19/115) were underweight (diencephalic syndrome), 16.5% (19/115) were overweight, and 6.1% of the patients (7/115) were obese.

The median age at follow-up was 12.6 years (range: 2.5–28.1). In total, 56.7% (80/141) children had entered puberty at follow-up, 14 were currently treated with puberty inhibition and four with estrogen or testosterone suppletion. At follow-up, 13.2% (17/129) of children had a height SDS below −2.0. Normal weight was present in 52.9% (81/153), underweight in 2.0% (3/153), overweight in 29.4% (45/153), and obesity in 15.7% (24/153). HS was present in 39.7% (52/131).

Prevalence of bone problems

Of the 161 patients, vertebral fractures were found in five of them. Of these five, one patient had vertebral fractures of grade I-II and four had a vertebral fracture of grade III. Of all, 99 patients had ever been assessed for bone health with DXA ($n=12$, 7.5%) or BHI ($n=95$, 59.0%). Of these 99, a total of 34 patients had very low BMD. Median BHI SDS of all measurements in patients with very low BMD was −3.0 (IQR −3.7 to −2.4, range −4.6 to −2.0) and median adjusted BMD *Z*-score on DXA scan was −3.8 (IQR −4.4 to −2.7, range −4.8 to −2.5) ($n=5$). Of all measured patients ($n=99$), median BHI SDS was −1.4 (IQR −2.4 to −0.4) and median adjusted BMD *Z*-score was −2.1 (−4.0 to −1.2).

Taken together, 36.3% of the patients (36/99) had developed a bone problem; two patients based on vertebral fractures grade III only, and all others based on very low BMD, of which three combined with a fracture. In total, 22.2% (22/99) patients showed BMD *Z*-score between −1 and −2 (low BMD) as assessed by BHI in 20 patients and by DXA scan in two patients. Treatment with bisphosphonates had been administered to one patient with a vertebral fracture and two patients with vertebral fracture of grade III.

Factors associated with bone problems

Children with bone problems ($n = 36$) were compared with children without bone problems, among those with measurements of BHI or BMD available ($n = 63$) (Table 1). Children with bone problems had a history of diencephalic syndrome (DS) more often (50.0% versus 10.0%, $P < 0.001$). Children with bone problems were more often blind (21.7% vs 5.6%) than children without bone problems, and more often severely or moderately visually impaired (8.7% vs 1.9% and 26.1% vs 11.1%, respectively) ($P = 0.004$). Weight problems associated with hypothalamic dysfunction were present more often in children with bone problems (62.5% vs 36.7%, $P = 0.038$). There was no difference in the number of patients with hypothalamic syndrome in children with bone problems compared to children without bone problems (for those with measurements available) (Supplementary Table 2) (Table 1).

In multivariable analysis, visual impairment was associated with bone problems (OR: 6.63, 95% CI: 1.83–24.00, $P = 0.004$) (Table 2).

Sensitivity analysis: all included children with supratentorial midline LGG

Sensitivity analysis was performed, including all patients ($n = 161$) (Supplementary Table 3). In this analysis, more bone problems were found in children with any neurosurgical intervention (72.2% vs 50.4%, $P = 0.023$). Pituitary dysfunction was more prevalent in children with bone problems (Fig. 1). Elevated IGF-1 (without GH replacement therapy) was more often present in children with a bone problem (42.4% vs 22.9%, $P = 0.044$). In children with bone problems, a total of 60.0% (15/25) had the hypothalamic syndrome compared to 34.9% (37/106) in children without bone problems ($P = 0.025$) (Table 3). Visual impairment was associated with bone problems in multivariable analysis (Supplementary Table 4).

Discussion

Adequate bone health is the prerequisite for normal bone development during childhood (28). Children with oncologic disease are at risk for impaired bone health, frailty, and sarcopenia (29), which in many cases may be prevented with adequate awareness, surveillance, and interventions. Despite multiple risk factors being present in children with supratentorial midline LGG, hardly any studies address this important issue. In our retrospective study, very low BMD was found to be highly prevalent in children with supratentorial midline LGG (34.3%), comparable with the prevalence of bone problems in pediatric chronic diseases (30).

Visual problems were associated with bone problems, most probably due to decreased mobility. We did not find any studies reporting on a higher risk for bone problems in otherwise healthy children with a visual handicap, but one may hypothesize that physical activity will be influenced. Increasing physical activity is considered to benefit BMD (31). The crude retrospective assessment of activity in our study does not reflect everyday life activity and should be studied more in-depth in future prospective studies. Other associations from univariate analysis were hypothalamic dysfunction (diencephalic syndrome at diagnosis and weight problems).

To our knowledge, the association between a history of diencephalic syndrome and a bone problem later in life has not been reported before. Of the children developing a bone problem, 50% has had the diencephalic syndrome. Multiple factors may underlie this association. The poor nutritional state at a young age in children with DS may be accountable for the process of deterioration of bone health at an early age. Similarly, patients with anorexia nervosa also experience deterioration of bone health, with osteoporosis reported in up to 20–30% (32). Next to low fat-mass, low calcium, and vitamin D status, a lower weight also affects physical mobility and therefore lower lean mass (33, 34, 35). The finding that bone health was still impaired after regaining weight in children with DS may be explained by the fact that the weight gain in children after DS is often exceptionally rapid with the development of hypothalamic overweight or obesity (36). Children with hypothalamic obesity often also show loss of initiative and decreased activity, contributing to poor bone health. Also, the fact that patients with elevated IGF-1 concentrations were at increased risk for a bone problem may be a reflection of hypothalamic damage and may be confounding to the presence of DS or age (37, 38). To correct for confounders, multivariable analysis was performed, which showed only vision loss as a significant associated factor for any bone problem. The association between vision loss and a bone problem may be caused by decreased physical activity (8, 39) or disturbance of the circadian rhythm due to visual impairment (7), or more likely, confounded by tumor location and hypothalamic involvement (40). Larger cohorts in future studies are needed to further evaluate the association between hypothalamic dysfunction and bone health.

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Table 1 Covariates in children with bone problems compared to without bone problems. Covariates in children with measurements of BMD/BHI specifically assessed for bone problems (*n* = 99). Definitions of all variables are attached in Supplementary 1. *P*-value for between-group differences calculated with Pearson chi-squared test and Fisher's exact test. If more than 20% of expected values were under five, Fisher's exact test was performed. For continuous variables (with non-normal distribution), the Mann–Whitney *U* test was used.

Covariate	Children with bone problems (%, *n*/*N*) *n* = 36	Children without bone problems (%, *n*/*N*) *n* = 63	*P*
Sex at birth, female	52.8% (19/36)	42.9% (27/63)	0.341
Age at brain tumor diagnosis, median in years (IQR) (range)	3.2 (0.6–7.9) (0.3–16.5)	4.4 (2.3–7.5) (0.6–15.5)	0.099
Follow-up time, median in years (IQR) (range)	3.6 (2.2–5.9) (0.0–13.9)	8.5 (5.1–13.3) (2.5–19.9)	<**0.001***
Muscle problems, yes	25.0% (5/20)	7.4% (4/54)	0.050
Inactivity			0.330
Relative	52.8% (19/36)	42.9% (27/63)	
Total	11.1% (4/36)	6.3% (4/63)	
Diencephalic syndrome history, yes	50.0% (13/26)	10.0% (5/50)	<**0.001***
Visual problems			**0.004***
No/mild	43.5% (10/23)	81.5% (44/54)	
Moderate	26.1% (6/23)	11.1% (6/54)	
Severe	8.7% (2/23)	1.9% (1/54)	
Blindness	21.7% (5/23)	5.6% (3/54)	
Vitamin D deficiency			0.145
Moderate	23.1% (3/13)	41.0% (16/39)	
Severe	23.1% (3/13)	35.9% (14/39)	
Pituitary dysfunction, Yes			
GH deficiency	22.2% (8/36)	14.3% (9/63)	0.314
ACTH deficiency	25.0% (9/36)	11.1% (7/63)	0.071
TSH deficiency	27.8% (10/36)	15.9% (10/63)	0.156
LH/FSH deficiency	2.8% (1/36)	3.2% (2/63)	0.912
Arginine vasopressin deficiency with thirst feeling	11.1% (4/36)	6.3% (4/63)	0.457
Arginine vasopressin deficiency without thirst feeling	8.3% (3/36)	1.6% (1/63)	0.135
No pituitary deficiency	63.9% (23/36)	77.8% (49/63)	0.136
CPP	38.5% (10/26)	43.8% (21/48)	0.660
Elevated IGF-1	42.4% (14/33)	25.4% (15/59)	0.092
Overweight at follow-up/time of bone problem	25.8% (8/31)	35.5% (22/62)	0.347
Obesity at follow-up/time of bone problem	12.9% (4/31)	16.1% (10/62)	0.682
Significant weight gain	50.0% (12/24)	36.0% (18/50)	0.251
ΔBMI SDS from diagnosis to follow-up, median (IQR) (full range)	2.2 (0.5–4.8) (−1.0–8.7)	1.3 (0.1–2.4) (−3.3–7.0)	0.116
Any clinical relevant weight problem associated with hypothalamic dysfunction**	62.5% (15/24)	36.7% (18/49)	**0.038***
Surgery treatment, yes	72.2% (26/36)	55.6% (35/63)	0.101
Number of surgeries, median (IQR) (range)	2 (1–2) (1–6)	2 (1–2) (1–4)	0.307
Chemotherapy, yes	72.2% (26/36)	74.6% (47/63)	0.796
Number of chemotherapy rounds, median (IQR) (range)	2 (1–3) (1–4)	2 (1–3) (1–5)	0.249
Targeted therapy	27.8% (10/36)	36.5% (23/63)	0.375
Trametinib	13.9% (5/36)	14.3% (9/63)	0.957
Tovorafenib	0.0% (0/36)	4.8% (3/63)	0.096
VCR neuropathy	25.0% (9/36)	22.2% (14/63)	0.753
Tumor recurrence or progression, Yes	74.3% (26/35)	82.5% (47/57)	0.347

***indicates a significant *P*-value ($P < 0.05$); **Any clinical relevant weight problem associated with hypothalamic dysfunction includes: diencephalic syndrome history or significant weight gain.

ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH/FSH, luteinizing hormone/follicle-stimulating hormone; TSH, thyroid-stimulating hormone.

Although not statistically significant in multivariable analysis, the prevalence of hypothalamic syndrome in the complete cohort of children with supratentorial midline LGG was higher in children with bone problems compared to children without bone problems. Hypothalamic dysfunction may negatively contribute to the homeostasis of the bone tissue (14, 17), which may be caused by pituitary insufficiency (GH or TSH deficiency), obesity, loss of initiative, and decreased mobility.

Table 2 Multivariable analysis of associated factors with bone problems. Multivariable analysis was done in the children specifically assessed for bone problems ($n = 99$). Definitions of all variables are attached in Supplementary 1. Weight problems includes: Diencephalic syndrome history or significant weight gain or overweight at follow-up or obesity at follow-up. Multivariable binary logistic regression. *P*-value calculated with Wald test.

Covariate	**All children** ($n = 66$) **OR** (95% CI)	***P***
Age at tumor diagnosis	1.02 (0.81–1.27)	0.891
Weight problems due to hypothalamic dysfunction or overweight/obesity at follow-up	1.68 (0.38–7.31)	0.493
Visual problems (moderate/severe/blindness vs none)	6.63 (1.83–24.00)	**0.004***

*indicates a significant *P*-value ($P < 0.05$).

Lastly, novel targeted therapies, such as RAF or MEK inhibitors, might contribute to bone resorption. Bone renewal no longer occurs sufficiently because cell growth and cell proliferation are inhibited (18, 19). As a result, the quality of the bone tissue decreases. In our study, however, trametinib and tovorafenib were not found to be univariately associated with bone problems. Also vincristine neuropathy was not associated with bone problems.

Limitations of the study

The design of this study may be considered a limitation, due to missing data. Questionnaires could not adequately assess inactivity and muscle problems because of the retrospective nature of this study. As most of the associations were tested univariately, no causal relationship can be drawn. Assessment of bone health during follow-up was not routinely assessed by DXA scanning, the current standard for determination of BMD (only available in 7.5% of the patients). It may be questioned whether the children without BMD or BHI measurements may have normal or lowered BMD as low BMD does not give any clinical signs and symptoms. There were apparently no clinical reasons for the treating physician to measure BMD or BHI and no reasons for the radiologist to suspect low bone quality after assessing the spinal images. Additionally, the fact that no x-ray of the hand had been performed may indicate that in these patients no longitudinal

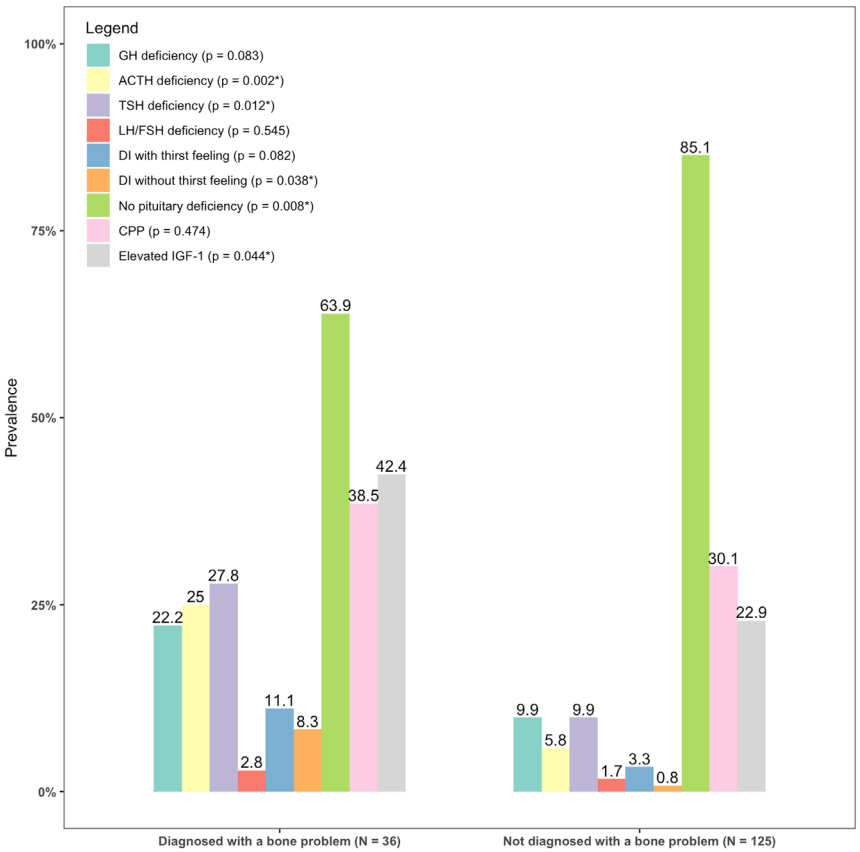

Figure 1

Pituitary deficiencies in children with and without bone problems. Number of pituitary deficiencies in children with clinical relevant bone problems compared to children without clinical relevant bone problems. *P*-value calculated with Wald test. ACTH, adrenocorticotropic hormone; DI, diabetes insipidus; GH, growth hormone; LH/FSH, luteinizing hormone/follicle-stimulating hormone; TSH, thyroid-stimulating hormone. *P*-value for between-group differences calculated with Pearson chi-squared test and Fisher's exact test. If more than 20% of expected values were under five, Fisher's exact test was performed instead of the chi-squared test.

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Table 3 Covariates of the hypothalamic syndrome in children with bone problems compared to without bone problems, in the whole cohort (*n* = 161). Definitions of all variables are attached in Supplementary 1. *P*-value for between-group differences calculated with Pearson chi-squared test and Fisher's exact test. If more than 20% of expected values were under five, Fisher's exact test was performed. For continuous variables (with non-normal distribution), the Mann–Whitney *U* test was used.

Covariate	Children with bone problems (%, *n*/*N*) *n* = 36	Children without bone problems (%, *n*/*N*) n = 125	*P*
Hypothalamic syndromeΩ, yes	60.0% (15/25)	34.9% (37/106)	**0.025***
Hyperphagia			0.248
Mild	25.0% (5/20)	19.0% (20/105)	
Severe	0.0% (0/20)	12.4% (13/105)	
Hypophagia			**0.001***
Mild	5.0% (1/20)	1.9% (2/104)	
Severe	20.0% (4/20)	1.0% (1/104)	
BMI			0.198
Normal weight or overweight	90.3% (28/31)	78.6% (92/117)	
Normal weight after specific intervention for hypothalamic obesity or overweight after specific intervention for hypothalamic obesity or obesity	9.7% (3/31)	21.4% (25/117)	
Behavioral problems			0.604
Mild	30.0% (6/20)	28.0% (26/93)	
Severe	0.0% (0/20)	7.5% (7/93)	
Sleep disorder			0.148
Mild	25.9% (7/27)	28.6% (32/112)	
Severe	33.3% (9/27)	17.0% (19/112)	
Temperature dysregulation			0.059
Mild	37.5% (3/8)	37.8% (17/45)	
Severe	25.0% (2/8)	2.2% (1/45)	
Pituitary dysfunction			**0.005***
Partial or complete pituitary dysfunction (with or without DI with adequate thirst feeling) or SIADH or history of central precocious puberty	45.7% (16/35)	28.9% (35/121)	
(Partial or complete) pituitary dysfunction including DI and adipsia (inadequate thirst feeling)	8.6% (3/35)	0.8% (1/121)	

ΩBased on the scoring of van Santen *et al* (1) (17).*Values in bold indicate statistical significance.

growth problems were present. Therefore, we expect it is reasonable to assume that these children did not have clinically relevant bone problems. However, bone problems can progress silently, and there may have been a misclassification bias in this case for which reason we first analyzed the 99 children with fractures or measured BMD and subsequently repeated the measurement in the total group. Both in the total group and in the 99 children with measurements of BMD/BHI, the same main findings in the multivariable analyses were found. It must be considered however, that also in the 99 cases with measurements of BMD/BHI, selection bias may have been present due to the fact that they had more frequent pituitary and hypothalamic problems. Patients referred to the endocrine department will have more frequent investigations of bone age than those without hypothalamic-pituitary (HP) dysfunction. This also explains that in the subgroup of 99 patients no differences were found in HP dysfunction between children with or without bone problems. It was not possible to draw any conclusions of the timing of bone problem development during follow-up, as no systematic measurements were done and digital x-ray radiogrammetry of the hand before 2010 did not contain the BHI.

Conclusion

Despite the limitations, our study provides new and valuable data on the prevalence and factors associated with bone problems in patients with supratentorial midline LGG. The prevalence of decreased bone health is high and the occurrence of bone problems in children with a supratentorial midline LGG may have a multifactorial origin. The results of our study may be used for future guideline development for surveillance and prevention of (severe) bone problems in patients with supratentorial midline LGG. Physicians should be aware of the risk for bone problems in children with supratentorial midline LGG, especially in case of visual problems and hypothalamic syndrome. Surveillance using DXA scans, supplementation of minerals and

vitamins important for bone health (vitamin D, calcium, but also folic acid and vitamin B12) (9), and optimal stimulation of physical activity (increasing mobilization, weight-bearing exercises, combined lifestyle programs, and if indicated referral to a physiotherapist) may help to prevent (further) bone loss in these children in the future (2). Physical therapy should be specifically designed and offered in cases of restricted visual capacity and lack of independent physical freedom and loss of initiative that may be encountered in patients with HS.

Future

Future research on bone health in LGG patients should ideally focus on prevalence and risk factors in prospective cohorts and pave the way to prevent BMD loss. To validate current findings, further studies are needed to evaluate the value of BHI using x-Ray of the hand with DXA, in this specific group of children. As children with a supratentorial midline tumor regularly undergo x-rays of the hand for endocrine evaluation purposes, this would be an ideal screening instrument for this group.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-24-0224.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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