Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma

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Abstract

Objective: Hypothalamic obesity in childhood craniopharyngioma (CP) patients carries a high risk for development of metabolic syndrome. In metabolic syndrome, the development of nonalcoholic fatty liver disease (NAFLD) is known. The aim of this study is to detect the risk for NAFLD in childhood-onset CP.

Design: This cross-sectional study included liver computed tomography (CT); ultrasound analysis of abdomen; measurements of serum parameters, height, weight and body composition; and daily medication of patients with childhood-onset CP.

Methods: A total of 384 patients recruited in trials HIT Endo and KRANIOPHARYNGEOM 2000 were analyzed. Ninety-four survivors were included by fulfilling the criteria of proven hypothalamic involvement (HI), a minimum time interval of 5 years between diagnosis and study, and a minimum age of 18 years at the time of evaluation. A total of 19 patients agreed to participate. To quantify the degree of steatosis hepatis, analyses of liver density were performed once by non-contrasted CT of liver sections.

Results: NAFLD occurs in about 50% of CP patients with HI and is associated with elevated liver enzymes and homeostasis model assessment index. BMI is not an effective predictive factor but body fat mass measured by near-infrared spectroscopy (NIRS) is. Over half of CP patients (60%) with NAFLD are treated with stimulating agents, with risk of hepatic side effects.

Conclusions: NAFLD is a major adverse late effect in childhood-onset CP. NIRS rather than BMI should be used to measure body composition and predict NAFLD. Stimulating agents for treatment of fatigue and daytime sleepiness in CP should be prescribed judiciously.

Introduction

Childhood-onset craniopharyngioma (CP) are rare intracranial embryonal malformations of the sellar region arising from remnants of Rathke’s pouch (1, 2). CP show low-grade histological malignancy (WHO 11) and frequently affect hypothalamic and pituitary regions due to their location. Hypothalamic involvement (HI) of CP resulting in pathological patterns of eating behavior and obesity are risk factors with major negative impact on prognosis and quality of life in surviving patients (1, 3, 4, 5, 6, 7, 8, 9, 10, 11). A striking problem in long-term survival is dealing with obesity-related comorbidities, which include diseases known as metabolic syndrome (12, 13). The metabolic syndrome associates obesity with high blood pressure, hyperlipidemia and pathological insulin resistance – the manifestation of type II diabetes mellitus (14). Not surprisingly, increased risk for the development of a nonalcoholic fatty liver disease (NAFLD) in these patients has been reported (15). Liver diseases of metabolic origin are associated with morbid obesity and are now considered the most prevalent liver diseases in Western countries (16).
The association between hypopituitarism, hypothalamic dysfunction and NAFLD was described in a retrospective study, which observed NAFLD in 2.3% of patients with hypopituitarism, hypothalamic obesity or CP (17). Also, a recent analysis of long-term outcomes of childhood onset CP found that one patient out of 32 (3%) passed away because of liver cirrhosis (7).

However, the risk for the development of NAFLD in childhood-onset CP patients suffering from hypothalamic obesity has not been investigated until now. In the present investigation we conducted a pilot study analyzing a small group of patients to assess the rate of NAFLD in patients with childhood CP and proven HI.

### Subjects and methods

#### Patients

For this study, 384 patients with childhood-onset CP, recruited in the German CP Registry (trials: HIT Endo, KRANIOPHARYNGEOM 2000; NCT00258453) to year-end 2006 were analyzed. Ninety-four surviving patients of those trials (24.5%) were included in this study, fulfilling our inclusion criteria: i) the existence of a HI, ii) a minimum time interval of 5 years between diagnosis and study and iii) a minimum age of 18 years at the time of evaluation.

One exception was made in the case of a 16-year-old girl who had received computed tomography (CT) liver examination for clinical reasons. Histological diagnosis of a CP was confirmed by reference assessment in all cases.

HI was defined as an involvement of hypothalamic structures due to the tumor growth and infiltration or due to damage of hypothalamic structures caused by surgical procedures. HI was confirmed by magnetic resonance imaging (MRI) and/or microscopic inspection during surgery. For practical reasons, we excluded patients without a valid address and patients with too long travel distances to our study center. In the end, we contacted 33 patients who fulfilled the above-mentioned inclusion criteria. Of these 33, 19 patients agreed to undertake a liver CT for assessment of NAFLD at our study center in Oldenburg, Germany. The study was performed between 2007 and 2009.

In addition to CT of the liver, an ultrasound analysis of the abdomen, serum parameters analyses of the liver and measurements of endocrine function, body composition, body fluid/body fat relation, height and weight were also performed. To assess the existence and degree of obesity, BMI was calculated and expressed as a SDS according to the references of Rolland-Cachera et al. (18). BMI was evaluated at the time of diagnosis and again during this study. For all patients except one, the development of BMI and medication during follow-up after 2–7 years (median 5 years) could be evaluated. Parameters of liver function could be evaluated in 17 patients during follow-up care.

The study was approved by an institutional ethics board and written parental and/or patient consent was obtained in all cases.

### CT liver diagnostics and sonography of the abdomen

To quantify the degree of liver steatosis, analyses of liver density were performed by non-contrasted CT (Siemens SOMATOM Emotion 6 CT scanner) of liver sections. A representative 10 mm thick single section was used for each patient, with an image quality of 130 kV tube voltage and quality reference mAs of 100. Inclusion of visually distinct vasculature and biliary structures in regions of interest was avoided (19). Images were reviewed by a single expert radiologist, blinded to clinical data, who determined hepatic attenuation with Hounsfield units (HU) of the liver (existence of fatty liver tissue leads to a direct proportionate decrease of HU in CT). Normal liver tissue was defined by mean HU > 45; moderate steatosis hepatis was defined as mean HU 20–45, and severe HU was defined as mean HU < 20 (20). The radiation dose of a CT liver section ranged from 0.1 mSv to 0.3 mSv.

Prior to CT analysis, all patients were examined by sonography of the abdomen. Due to diagnostic difficulties caused by the thickness of the abdominal wall in obese patients, no reliable sonographic assessment of existence or extent of steatosis hepatis could be achieved (data not shown).

### Assessment of body fluid/body fat relation by near-infrared spectroscopy

Body fluid/body fat relation (composition measurement) was measured with near-infrared spectroscopy (NIRS) (FUTREX 5000 analyzer, Gaithersburg, MD, USA). The NIRS technique was used as it has been reported to be a fast, accurate and low cost method for determining human body fat content (21). Also, the NIRS interactance measurements of fat mass have been shown to correlate significantly with dual-energy x-ray absorptiometry measured body fat mass (22). NIRS interactance measurements were performed by placing a FUTREX sensor on the upper arm for several seconds and then entering patient data on birth, gender, height and weight as well as information about type of bone structure and level of
physical activity. Body fluid proportion was then calculated by the analyzer based on a normal content of fluid in fat-free tissue (23).

**Blood serum parameters**

Fasting blood sampling was performed on 12 patients; non-fasting samples were collected from seven patients. Following withdrawal, serum samples were put on ice and immediately centrifuged. Very low density lipoprotein (VLDL) cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol were determined by a commercial lipid electrophoresis kit (Sebia, Norcross, GA, USA). Aspartate and alanine aminotransferase (AST and ALT), glutamate dehydrogenase (GLDH), cholinesterase (ChE), gamma glutamyl transferase (GGT), bilirubin, blood glucose, cholesterol and triglycerides were measured by a commercial serum analyzer system (COBAS INTEGRA, Roche Diagnostics). The Quick and partial thromboplastin time (PTT) coagulation parameters were calculated by optical clotting test (BCS XP, Siemens Healthcare Diagnostics, Eschborn, Germany). Plasma insulin concentrations were measured by microparticle enhanced immunometric assay (MEIA, Abbott). HbA1c was analyzed by a HPLC-filtration system (D-10, Bio-Rad Laboratories). Insulin resistance was assessed by homeostatic model assessment (HOMA), which is based on fasting glucose and insulin concentrations using the following formula: resistance (HOMA) = (insulin (mU/l) × glucose (mg/dl))/405.

**Statistical analyses**

Statistical analyses were performed using SPSS 19.0 (SPSS, Inc.). For comparison of two independent groups for a continuous variable, the Mann–Whitney U-test was used. For comparison of two related groups for a continuous variable, the Wilcoxon Signed Rank test was used. For comparison of different groups for categorical variables, the χ² test was used. P values of <0.05 were chosen as being statistically significant.

**Results**

According to measurements of liver density in the liver CT analyses, ten out of 19 patients in our cohort were identified with steatosis hepatis – three of them with severe steatosis hepatis (mean HU <20) and seven with a moderate steatosis (mean HU 20–45). Nine patients turned out to have normal liver density (mean HU >45), which meant no fatty liver disease. Figure 1 depicts representative CT imaging for both steatosis hepatis conditions: one patient with and one patient without steatosis hepatis. Patients with steatosis hepatis did not differ in terms of gender or age at diagnosis, evaluation and follow-up, as compared to patients without steatosis hepatis (Table 1). All patients presented with HI of the CP due to study

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**Figure 1**

Computed tomography liver imaging of (a) a patient with severe steatosis hepatis and (b) with a normal liver. Circles depict the regions of interest in which Hounsfield units (HU) are measured.
inclusion criteria. In addition, BMI at diagnosis as well as BMI at evaluation did not differ between patients with steatosis hepatis and patients with normal CT liver findings (Table 1). Prior to CT analysis, all patients were examined by ultrasonography of the abdomen. Due to diagnostic difficulties caused by the thickness of the abdominal wall in obese patients, no reliable assessment of existence or extent of steatosis hepatis could be achieved by ultrasonographic analyses (data not shown).

Regarding analyses of blood samples taken from all study patients, statistically significant differences between patients with and without steatosis hepatis were detected for serum concentrations of AST, GLDH, GGT and insulin, with more pathological findings for patients with steatosis hepatis (Table 2). Similarly, the measurement of body fat by near-NIRS showed a higher amount of total body fat in patients with CT findings of steatosis hepatis when compared to patients without steatosis hepatis (Table 1). In 11 patients (57.9%) it was possible to assess insulin resistance by the calculation of the HOMA index based on fasting glucose and insulin concentrations. It was not possible to perform the HOMA on all 11 patients because

### Table 1
Characteristics of 19 patients with childhood-onset craniopharyngioma (CP) recruited in HIT Endo and KRANIOPHARYNGEOM 2000 trials at time of CP diagnosis and current study. BMI–SDS was calculated according to Rolland-Cachera et al. (18). Bold-formatting indicates significant differences.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients without steatosis hepatis</th>
<th>Patients with steatosis hepatis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years), median (range)</td>
<td>11.9 (2.8–20.5)</td>
<td>9.39 (5.06–19.6)</td>
<td>0.859</td>
</tr>
<tr>
<td>Age at study (years), median (range)</td>
<td>23.7 (18.9–29.2)</td>
<td>25.16 (16.9–30.3)</td>
<td>0.591</td>
</tr>
<tr>
<td>Follow-up interval (years), median (range)</td>
<td>12.8 (6.0–24.1)</td>
<td>14.7 (6.1–19.1)</td>
<td>0.765</td>
</tr>
<tr>
<td>Gender, n (male/female)</td>
<td>4/5</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>Degree of resection, n (%)</td>
<td>3 (32.4)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>6 (66.7)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>Hypothalamic involvement, n (%)</td>
<td>9 (100)</td>
<td>10 (100)</td>
<td></td>
</tr>
<tr>
<td>BMI–SDS at diagnosis, median (range)</td>
<td>0.66 (–0.6–4.67)</td>
<td>0.70 (–1.6–3.65)</td>
<td>0.530</td>
</tr>
<tr>
<td>BMI–SDS at study, median (range)</td>
<td>5.48 (1.51–10.29)</td>
<td>7.30 (3.71–12.62)</td>
<td>0.331</td>
</tr>
<tr>
<td>Body composition, %, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fluid</td>
<td>49.90 (41.00–56.70)</td>
<td>45.30 (36.70–51.60)</td>
<td>0.036</td>
</tr>
<tr>
<td>Body fat</td>
<td>35.35 (23.90–49.30)</td>
<td>42.60 (32.90–55.80)</td>
<td>0.033</td>
</tr>
<tr>
<td>Hounsfield units (HU), median (range)</td>
<td>57 (46–63)</td>
<td>32 (15–41)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2
Serum parameters of 19 patients with childhood-onset craniopharyngioma (CP) recruited in HIT Endo and KRANIOPHARYNGEOM 2000 at time of study. Bold-formatting indicates significant differences.

<table>
<thead>
<tr>
<th>Serum parameters</th>
<th>Patients without steatosis hepatis</th>
<th>Patients with steatosis hepatis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Median (range)</td>
<td>n</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>8</td>
<td>177 (144–263)</td>
<td>10</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>8</td>
<td>40 (26–58)</td>
<td>10</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>8</td>
<td>119 (86–213)</td>
<td>10</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>8</td>
<td>9.5 (6–20)</td>
<td>10</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>8</td>
<td>178.5 (115–271)</td>
<td>10</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>9</td>
<td>29 (21–39)</td>
<td>10</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>9</td>
<td>28 (13–62)</td>
<td>10</td>
</tr>
<tr>
<td>GLDH (U/l)</td>
<td>9</td>
<td>2.95 (0.3–7)</td>
<td>10</td>
</tr>
<tr>
<td>CHE (U/l)</td>
<td>9</td>
<td>9.95 (7–11.9)</td>
<td>10</td>
</tr>
<tr>
<td>Gamma-GT (U/l)</td>
<td>8</td>
<td>23 (7.8–99)</td>
<td>10</td>
</tr>
<tr>
<td>Quick (%)</td>
<td>8</td>
<td>103.5 (95–112)</td>
<td>10</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>8</td>
<td>25.5 (22–39)</td>
<td>10</td>
</tr>
<tr>
<td>Billirubin (mg/dl)</td>
<td>9</td>
<td>0.55 (0.2–1.7)</td>
<td>10</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>9</td>
<td>17.15 (2.3–36.2)</td>
<td>9</td>
</tr>
<tr>
<td>HbA1C (% of Hb)</td>
<td>9</td>
<td>5.2 (4.5–7.0)</td>
<td>10</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>9</td>
<td>75 (58–101)</td>
<td>10</td>
</tr>
<tr>
<td>HOMA</td>
<td>6</td>
<td>2.45 (0.3–5.5)</td>
<td>5</td>
</tr>
</tbody>
</table>

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the fasting condition was not given. Due to long travelling
distances and existing eating disorders such as hyper-
phagia, fasting blood analysis could not be achieved in
some cases. Five patients with steatosis hepatis (50%)
showed a significantly higher HOMA index when
compared to six of the nine patients with normal liver
CT (P = 0.036) (Table 2).

We asked all patients to report their regular daily
medication. All patients received hormonal substitution
for desmopressin and all patients with the exception of
one were on hormonal substitution of hydrocortisone,
L-thyroxine and sex steroids. Twelve (63%) of our patients
received recombinant growth hormone, without any
differences between patients with or without steatosis
hepatitis. However, we found a striking difference concern-
ing additional medication. Half (five out of ten) of our
patients with steatosis hepatitis were treated with the wake-
promoting agents methylphenidate or modafinil, likely
administered to treat excessive daytime sleepiness and
severe fatigue due to secondary narcolepsy. No patient
without steatosis hepatitis was treated by such stimulating
agents. Four patients (44%) in the group without steatosis
hepatitis were treated with melatonin for regulation of
circadian rhythms (24) (Table 3).

Since the evaluation of our patients was performed
between 2007 and 2009, we were able to analyze these
patients during longitudinal follow-up. We analyzed BMI,
blood parameters and medication after a follow-up period
of 2–7 years (Tables 4 and 5). Differences between patients
with and without steatosis hepatitis were detected for serum
concentrations of AST and GGT, with more pathological
findings for patients with steatosis hepatitis. Again, no
significant differences were detected in BMI. At the last
follow-up visit, the number of patients treated with
methylphenidate or modafinil in the steatosis hepatis
group rose to six patients out of ten: one was additionally
receiving melatonin and one patient stopped treatment
with methylphenidate. As was the case during the original
evaluation, at the last follow-up visit no patient without
steatosis hepatitis was treated with methylphenidate or
modafinil. The rate of medication for diabetes mellitus
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with and without steatosis hepatitis were detected for serum
concentrations of AST and GGT, with more pathological
findings for patients with steatosis hepatitis. Again, no
Table 3 Medication of the 19 patients with childhood-onset
craniopharyngioma (CP) recruited in HIT Endo and KRANIO-
PHARYNGEOM 2000 trials at the time of current study.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients without steatosis hepatitis</th>
<th>Patients with steatosis hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Cortisone</td>
<td>8 89</td>
<td>10 100</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>9 100</td>
<td>10 100</td>
</tr>
<tr>
<td>L-thyroxine</td>
<td>8 89</td>
<td>10 100</td>
</tr>
<tr>
<td>Rec. growth hormone</td>
<td>6 67</td>
<td>6 60</td>
</tr>
<tr>
<td>Sex steroids</td>
<td>8 89</td>
<td>10 100</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0 0</td>
<td>5 50</td>
</tr>
<tr>
<td>Melatonin</td>
<td>4 44</td>
<td>0 0</td>
</tr>
<tr>
<td>Anti-diabetic drugs</td>
<td>0 0</td>
<td>1 10</td>
</tr>
<tr>
<td>Cardiac medicine</td>
<td>0 0</td>
<td>2 20</td>
</tr>
</tbody>
</table>

Rec. growth hormone, recombinant-growth hormone (rec-hGH).

Table 4 Follow-up of the 19 patients with childhood-onset craniopharyngioma (CP) recruited in HIT Endo and KRANIO-
PHARYNGEOM 2000 during follow-up 2–7 years after original study (liver CT diagnostic). Bold formatting indicates significant differences.

<table>
<thead>
<tr>
<th>Serum parameters</th>
<th>Patients without steatosis hepatitis</th>
<th>Patients with steatosis hepatitis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (range)</td>
<td>n</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>9</td>
<td>193 (145–238)</td>
<td>9</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>9</td>
<td>41 (31–74)</td>
<td>8</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>9</td>
<td>135 (76–185)</td>
<td>8</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>9</td>
<td>14 (2–28)</td>
<td>6</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>9</td>
<td>199 (98–293)</td>
<td>9</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>9</td>
<td>24 (17–44)</td>
<td>8</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>9</td>
<td>22 (14–102)</td>
<td>8</td>
</tr>
<tr>
<td>GLDH (U/l)</td>
<td>9</td>
<td>3 (3–5.8)</td>
<td>5</td>
</tr>
<tr>
<td>ChE (U/l)</td>
<td>9</td>
<td>9.3 (7–12.7)</td>
<td>6</td>
</tr>
<tr>
<td>Gamma-GT (U/l)</td>
<td>9</td>
<td>28 (17–77)</td>
<td>7</td>
</tr>
<tr>
<td>Quick (%)</td>
<td>6</td>
<td>105 (98–118)</td>
<td>7</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>6</td>
<td>28 (22–32)</td>
<td>7</td>
</tr>
<tr>
<td>Billirubin (mg/dl)</td>
<td>8</td>
<td>0.3 (0.1–1.9)</td>
<td>6</td>
</tr>
<tr>
<td>HbA1c (% of Hb)</td>
<td>8</td>
<td>5.45 (4.6–7.4)</td>
<td>8</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>8</td>
<td>84.5 (67–227)</td>
<td>7</td>
</tr>
<tr>
<td>BMI–SDS</td>
<td>9</td>
<td>4.35 (1.12–10.85)</td>
<td>9</td>
</tr>
</tbody>
</table>
Table 5 Medication of 19 patients with childhood-onset craniopharyngioma (CP) recruited in HIT Endo and KRA
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<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients without steatosis hepatis</th>
<th>Patients with steatosis hepatis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cortisone</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>t-Thyroxine</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>*Rec. growth hormone</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Sex steroids</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Melatonin</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Anti-diabetic drugs</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Cardiac medicine</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>

Rec. growth hormone, recombinant-growth hormone (rec-hGH).

hypothalamic dysfunction of different origins found NAFLD in 2.3% of patients’ liver biopsies or abnormal liver enzymes imaging studies (17). Our study shows that the rate of NAFLD is even higher in CP survivors due to obesity caused by HI, which studies have shown can be caused by the CP tumor itself and/or by hypothalamic damage caused by its surgical treatment (3, 13, 33, 34). Signs of steatosis hepatis were not associated with BMI in our study cohort. However, a significant association was found between steatosis hepatis, elevated liver enzymes and a higher body fat proportion respectively. The observation that development of NAFLD in our cohort was not associated with increased BMI might be explained by the identification of metabolically benign obesity in humans (35) as well as a higher correlation of fatty liver disease and impaired glycemic status (36). Studies of patients with NAFLD have demonstrated that insulin resistance and pathologic HOMA might be predictors or at least associated with the development of a NAFLD (37, 38), which our study confirmed for our cohort. In addition, we found a significant association between NAFLD and elevated liver enzymes as well as a higher body fat proportion, which is in line with findings of patients without CP but with metabolic syndrome and NAFLD (39). The high rate of NAFLD we found in about 50% of CP patients with HI is higher than previous estimates and indicates that the monitoring of liver function is a critically important component in follow-up care of CP patients. This can be performed reliably yet noninvasively using the combination of liver enzyme monitoring and liver imaging in follow-up care. In patients with signs of steatosis hepatis, liver function should be even more closely monitored to estimate the degree of hepatic damage. Liver-toxic drugs should be avoided. In case of impaired liver function, dose modifications are necessary in order to adjust medication to prolonged hepatic drug metabolism. A liver biopsy to calculate the risk for steatohepatitis (NASH) or liver cirrhosis should be considered on an individual basis. Assessment of steatosis hepatis using MRI would be an alternative, which is less invasive in terms of radiation load and practicable in the context of MRI follow-up monitoring of CP (40).

An unexpected finding was the high rate of patients treated with methylphenidate or modafinil in the group of patients with steatosis hepatis. Methylphenidate is widely used in the treatment of children with attention deficit hyperactivity disorder (41) and is also used, as is modafinil, to treat secondary narcolepsy and severe daytime sleepiness in CP patients (42). Our original evaluation found 50% of our patients with steatosis hepatis were

Discussion

NAFLD is currently the most common liver disease worldwide (16), its pathology ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) (16). NAFLD is strongly linked to obesity, with a reported prevalence of 80% in obese patients but only 16% in individuals with a normal BMI and without metabolic risk factors (25). Because long-term survival of childhood CP is often associated with hypothalamic obesity, leading to severe long-term sequelae and comorbidities (5, 26, 27, 28, 29, 30, 31, 32), we analyzed the rate of NAFLD in childhood-onset CP patients with HI. In our group of 19 patients, we observed CT findings typical for steatosis hepatis in about 50% of all cases. This indicates a significant risk to patients with CP and HI of developing NAFLD. A previous retrospective analysis of patients with steatosis hepatis. These five included two patients treated with metformin, one patient treated with sulfonylurea plus dipeptidyl peptidase-4 inhibitor and two patients treated with sulfonylurea plus SGLT-2-inhibitor plus subcutaneously injected insulin analogon (insulin glargine). The rate of medication for hypertension/heart failure (β blocker, ACE inhibitors) increased from one patient at the original evaluation to five patients at the last follow-up, with similar distribution for both groups of patients with and without steatosis hepatis (Table 5). Two patients in the steatosis hepatis group died in the meantime due to complications caused by acute adrenal insufficiency. Importantly, clinical symptoms of liver cirrhosis have not been observed in any of our patients.

Discussion

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being treated with such agents and in the follow-up analysis the rate was even higher (60%). In contrast, no patient without steatosis hepatis was treated with methylphenidate or modafinil. This is the first study that demonstrates the coexistence of treatment with methylphenidate or modafinil and the development of a NAFLD in CP patients. Side effects of methylphenidate or modafinil are commonly reported to be loss of appetite, anxiety as well as increase in blood pressure and even accelerated heart rate that in some cases has led to sudden cardiac death (43, 44). Treatment using these agents has also caused hepatotoxicity, mostly as a development of mild, asymptomatic and reversible elevation of liver chemistries (45). However, a much more severe case report was recently published describing an acute methylphenidate-induced liver failure, which needed to be treated by liver transplant (45). The suggestion for the mechanism of liver injury in this case was direct toxicity of methylphenidate to hepatocytes as an idiosyncratic reaction (42). These reports suggest a risk of liver damage by methylphenidate treatment in patients with NAFLD. In our cohort, at least two of our patients first developed NAFLD and then started treatment with methylphenidate afterwards. Taking this into account, treatment with stimulating agents should be considered a risk rather than a direct cause of liver damage, administered on a case-by-case basis.

In patients with impaired liver function, treatment with methylphenidate should be stopped. Alternative medication for secondary narcolepsy and daytime sleepiness with lower potential hepatic toxicity (such as modafinil) should be considered. The dosage of alternative medication should be escalated slowly until the desired clinical effect has been reached. In case of impaired liver function, dose modifications are necessary in order to adjust medication to prolonged drug metabolism.

It is possible that the disturbance of circadian rhythms, which is a known phenomenon in CP patients with HI (42, 46), is worsened by liver disease, aggravating the severe clinical symptoms of secondary narcolepsy such as daytime sleepiness. Sleep disorders, fatigue and daytime somnolence are also known symptoms for other types of chronic liver diseases such as cirrhosis, chronic hepatitis C, Wilson disease and NAFLD itself (47).

The limitations of our study are related to the small patient cohort that we were able to analyze, even though these patients were part of a much larger cohort of two CP clinical trials with high degrees of recruiting completeness. To avoid examinations more invasive than CT scans – which many candidate patients still declined to undergo – we resigned not to undertake liver biopsies for more detailed information about their liver state. The question whether prevention, early detection and treatment of steatosis hepatis have beneficial effects on the outcome and quality of life in CP cannot be answered for our patient cohort. A close monitoring of patients at risk for hepatotoxicity is part of our follow-up protocol. Hopefully, this question will be answered based on longitudinal analyses of the outcome and quality of life in the context of our CP registry.

Conclusions

NAFLD occurs in about 50% of CP patients with HI and should be planned for and managed as a major adverse late effect in follow-up care of CP patients. Since BMI as an assessment of body fat mass is not an effective predictive factor for the development of a NAFLD but NIRS is, careful monitoring of the risk of NAFLD using NIRS is suggested. When the monitoring of liver function shows signs of impaired liver function or imaging findings indicate steatosis hepatis, liver biopsy should be considered. Because a high number of CP patients (60%) with NAFLD are treated with stimulating agents to treat daytime sleepiness and severe fatigue due to secondary narcolepsy – but an increased risk of liver damage by methylphenidate treatment in patients with NAFLD cannot be excluded – alternative medication with lower hepatic toxicity should be considered.

Declaration of interest

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Author contribution statement

A Hoffmann designed the cross-sectional study, evaluated patients’ records, did the statistical analyses, wrote and reviewed the manuscript. K Bootsvoeld performed the computed tomographies of the patients as a radiologist, participated in designing the study, evaluating patients’ records, writing and reviewing the manuscript. U Gebhardt supervised statistical analyses, did the graphical work on figures and reviewed the manuscript. A M Daubenbüchel supervised data evaluation, performed statistical analyses, and reviewed the manuscript. A S Sterkenburg participated in designing the study, evaluating patients’ records, writing and reviewing the manuscript. H L Müller initiated the study, participated in evaluation of patients’ records, supervised plausibility controls and...
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**Clinical Study**

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