의학석사 학위논문

Development of nonalcoholic fatty liver disease after treatment in patients of childhood-onset craniopharyngioma

소아기에 발생한 두개인두종 환자에서 치료 후 비알코올성 지방간 발생에 관한 연구

2017년 2월

서울대학교 대학원

임상의과학과

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지도 교수 신 충 호

이 논문을 의학석사 학위논문으로 제출함
2016 년 10 월

서울대학교 대학원

임상의과학과

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정소윤의 석사학위논문을 인준함
2016 년 12 월

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Abstract

Development of nonalcoholic fatty liver disease after treatment in patients of childhood-onset craniopharyngioma

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Purpose: Hypothalamic obesity in childhood-onset (co-) craniopharyngioma patients may predispose to nonalcoholic fatty liver disease (NAFLD). This study reviewed the characteristics of NAFLD associated with co-craniopharyngioma.

Methods: This study retrospectively reviewed 75 patients who underwent surgery for craniopharyngioma while younger than 15 years of age between 2000 and 2016.

Results: Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 40 IU/L was observed in 51 of the 75 (68%) co-craniopharyngioma patients. Imaging studies were performed for 32 patients with elevated liver enzymes. The estimated prevalence of NAFLD in co-craniopharyngioma was 47%. NAFLD was detected in 22 patients (male 59%, 4.3±4.0 years after first surgery). The mean age at the time of the initial operation was 9.1±2.9 years. Six patients (27.3%) were diagnosed within one year. Among the 19 patients with initial height and weight data, the body mass index (BMI) z-score (BMI_Z) at the time of diagnosis of NAFLD was 1.37±1.01 (range −0.75 to 3.18), with 4 (18.2%) patients being overweight and 9 (40.9%) being obese. BMI_Z increased above that at the time of the operation for 13 patients (68.4%) by 1.13 (range 0.10–2.84). Seventeen patients did not receive growth hormone. Insulin-like growth factor-I level < 3rd percentile was observed in 19 patients.

Conclusion: NAFLD is common in survivors of co-craniopharyngioma and may develop earlier. If ALT or AST is above 40 IU/L, a diagnostic work-up should be started.

Keywords: child craniopharyngioma, nonalcoholic fatty liver disease, growth hormone deficiency, hypothalamus, obesity

Student Number: 2015-22259

CONTENTS

Introduction

Craniopharyngiomas are rare sellar malformations with low histological grade. Between 30% and 50% of all cases are diagnosed in children and adolescents, and childhood-onset (co-)craniopharyngioma comprises 1.2-4% of all childhood intracranial tumors, making it the most common pituitary mass in childhood[1,2]. Craniopharyngioma patients suffer from visual impairment, anterior and posterior hormone deficiencies, and severe obesity after tumor resection surgery[1]. Craniopharyngiomas can cause metabolic syndrome as a result of central obesity, increased insulin resistance, increased blood pressure, hyperlipidemia, and growth hormone deficiency or inactivity[3-5].

As the prevalence of pediatric obesity increases, nonalcoholic fatty liver disease (NAFLD) is also increasing in children and adolescents in many developed countries. Although the prevalence of NAFLD in children varies widely depending on the diagnostic methods used, several studies have reported prevalence of 3-10% in general pediatric populations[6], increasing to 50% in co-craniopharyngioma patients with hypothalamic involvement[7]. NAFLD is defined as excessive

deposition of fat in the liver, leading to a spectrum of hepatic pathologies ranging from simple steatosis in the most benign form to nonalcoholic steatohepatitis (NASH) or cirrhosis in the absence of significant alcohol consumption[6,8]. Traditionally, fructose ingestion, visceral obesity, insulin resistance, and metabolic syndrome are considered risk factors for NAFLD[6,8]. Oxidative stress, lipotoxicity, adipocytokines, mitochondrial dysfunction, endoplasmic reticulum stress[6], and bisphenol A[9] have all been implicated. NAFLD may also coincide with endocrine diseases, such as polycystic ovary syndrome, hypothyroidism, growth hormone deficiency, or hypercortisolism[10,11].

Severe hypothalamic obesity has significant negative impact on metabolic function including NAFLD and quality of life in long-term survivors of co-craniopharyngioma[12-14]. NAFLD proved by computed tomography (CT) occurs in about 50% of young adults with co-craniopharyngioma and is associated with elevated liver enzymes[7].

Thus, it is essential to understand the characteristics of co-craniopharyngioma patients to prevent development of NAFLD and improve their quality of life. This study describes the clinical characteristics of NAFLD in co-craniopharyngioma patients, including frequency, time interval, and predictive

factors.

Materials and methods

1. Subjects

Medical records of craniopharyngioma patients from Seoul National University Children' s Hospital were retrospectively reviewed. During the years reviewed, the goal of the surgery was always radical excision whenever possible. We reviewed 76 patients who had their first surgery before the age of 15 years from 1 January, 2000 to 1 February, 2016 (Fig. 1).

In our institute, liver imaging studies are not routinely performed for craniopharyngioma patients. For the 75 patients reviewed, 32 underwent imaging studies due to elevated liver enzymes. Ultimately, 22 patients were diagnosed with NAFLD based on the imaging studies, and we reviewed the clinical courses of these patients. The current study was approved by the Seoul National University Hospital Institutional Review Board (IRB No. 1608-141-787).

2. Hormone replacement

All patients were preoperatively evaluated regarding the need for replacement therapy with levothyroxine, hydrocortisone,

and antidiuretic hormone (ADH)[14]. Postoperatively, hydrocortisone was tapered to a tolerable dose under 15 mg/m^2/day and thyroid hormone was adjusted according to the free T4 level. Patients who had diabetes insipidus were placed on ADH replacement. Pituitary function tests including growth hormone (GH) were performed within 1 year post tumor surgery. If the patient agreed to take GH, GH for stature growth (0.5–0.7 mg/m^2/week) or GH for metabolic effect (0.1 mg/m^2/week) was started approximately 1 year after final tumor treatment whenever there was no tumor recurrence. Hypogonadotropic hypogonadism was evaluated after the age of 10 years for females or 12 years for males. All patients had GH deficiency, hypothyroidism, adrenal insufficiency, and DI. Hypogonadism was observed in 21 patients and the gonadal axis was not studied in the remaining case.

3. Demographics and laboratory assessment

Height was measured twice using a Harpenden stadiometer (Holtain, Crymych, UK) and weight was measured using a digital scale. The z-scores of height (height_Z), weight (weight_Z), and body mass index (BMI_Z) were calculated using the 2007 Korean National Growth Charts[15]. The serum

aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured and the normal ranges were 0–40 IU/L for both. NAFLD diagnosis was based on evidence of fatty liver from liver sonography or abdominal CT. Insulin–like growth factor–I (IGF–I) level < 3rd percentile was assigned using the Korean data[16].

4. Statistical analysis

All statistical analyses were conducted with IBM SPSS Statistics ver. 20.0 (IBM, Armonk, NY, USA). All continuous variables are described as mean ± standard deviation.

Results

AST or ALT elevation above 40 IU/L was observed in 51 of the 75 (68.0%) co-craniopharyngioma patients (Fig. 1). Imaging studies were performed for 32 patients with elevated liver enzymes, and NAFLD was detected in 22 patients by CT (n=5) or sonography (n=17). The estimated prevalence of NAFLD in co-craniopharyngioma was 46.8% [51 × (22/32) / 75]. NAFLD was not detected in 10 patients who underwent liver sonography. Only one patient (C11) had a liver biopsy, which proved to be NASH.

Clinical characteristics of NAFLD patients at initial operation

Of the 22 NAFLD patients, 13 (59.1%) were male (Table 1). The mean age at the time of the initial operation was 9.1±2.9 years. Preoperative anthropometric data were known in 19 cases. For these 19 patients, preoperative height z-score was −1.17±0.87, with 4 (21.1%) patients height_Z < −2; and BMI_Z of the 19 patients was 0.87±1.22, with 3 (15.8%) patients being overweight and 7 (36.8%) patients being obese.

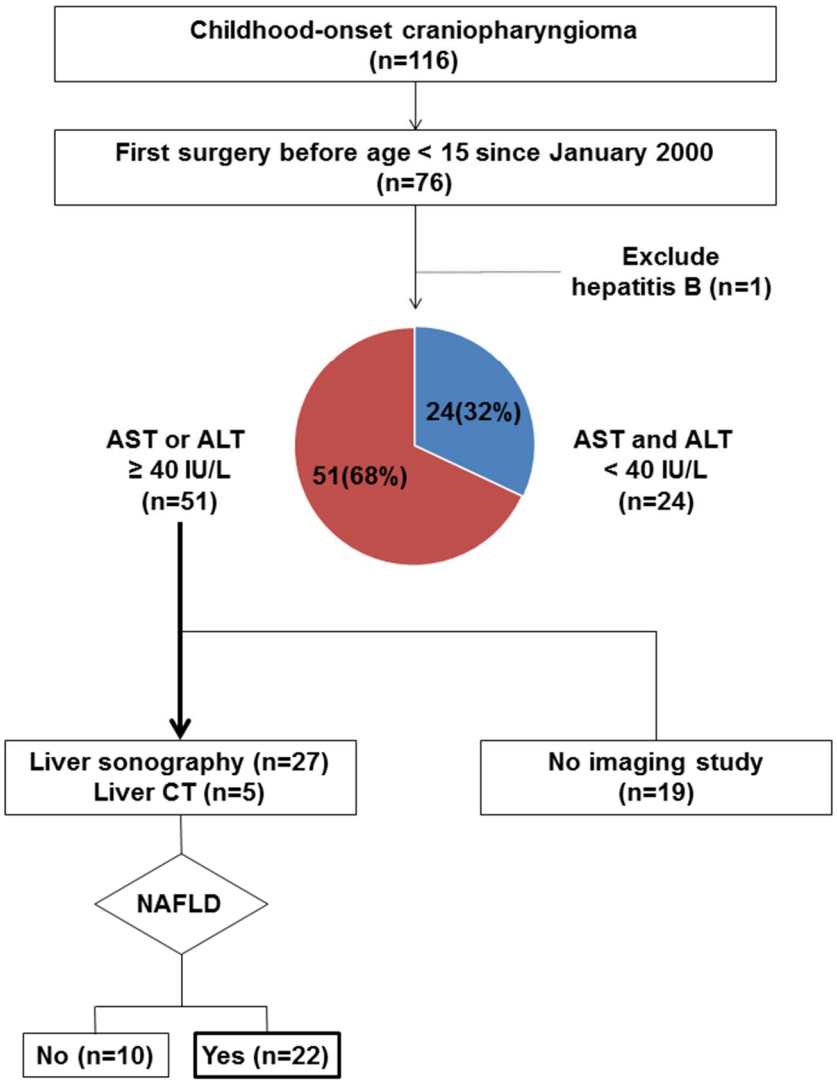
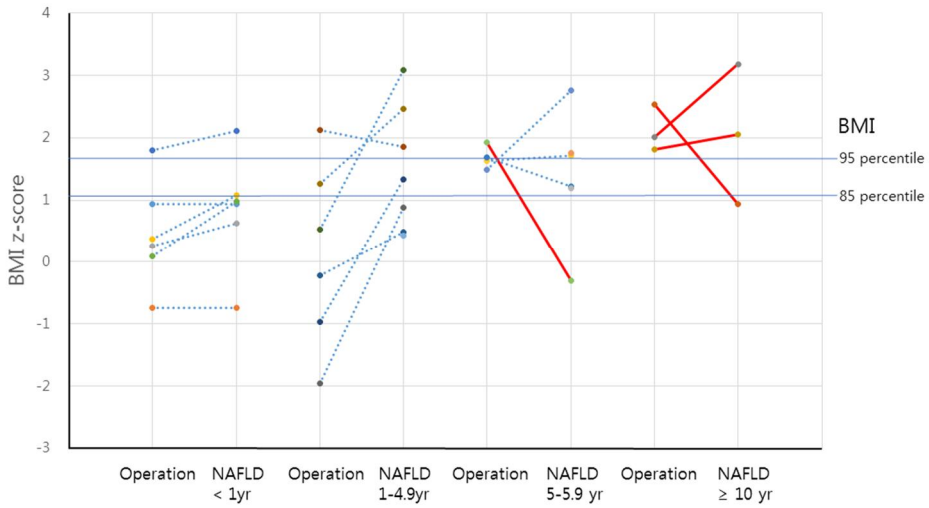


Fig 1. Study population. We reviewed 76 patients who had their first surgery before the age of 15 years from 1 January, 2000 to 1 February, 2016. Out of 75 patients, 32 underwent imaging studies because of elevated liver enzymes. Ultimately, 22 patients were diagnosed with NAFLD based on the imaging studies. The estimated prevalence of NAFLD in co-craniopharyngioma was 46.8%.

Clinical characteristics at diagnosis of NAFLD

The mean time interval to NAFLD diagnosis after initial surgery for the 22 diagnosed patients was 4.3±4.0 (range 0–12.2) years (Table 1). At the time of NAFLD diagnosis, BMI_Z was 1.37±1.01, with 4 (18.2%) patients overweight and 9 (40.9%) patients obese. For the 19 patients with initial height and weight data, BMI_Z increased post operation for 13 patients (68.4%) (Fig. 2) by 1.13 (range 0.10–2.84). The height_Z at the time of diagnosis of NAFLD was −0.40±1.35 (range −2.82 to 2.34)



(Fig. 3).

Fig 2. Body mass index (BMI) z score changes after initial operation. The red lines show the case was administered GH at NAFLD diagnosis. BMI_Z increased post operation for 13 patients (68.4%) by 1.13 (range 0.10–2.84).

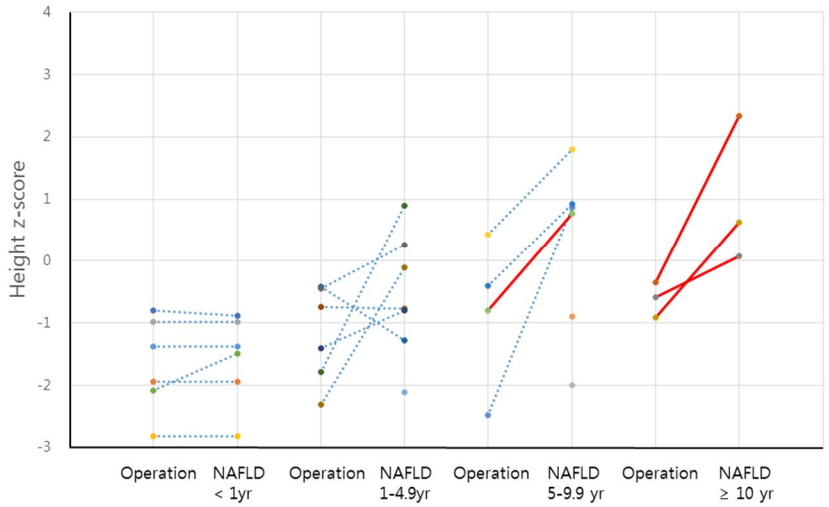


Fig 3. Height z score (height_Z) changes after initial operation. The red lines show the case was administered GH at NAFLD diagnosis. Preoperative height_Z was −1.17±0.87.

Six patients (C01–C06, 27.3%) were diagnosed with NAFLD within 1 year. One was diagnosed preoperatively and three patients were diagnosed within 1 month (4, 11, and 19 days) postoperatively. All were administered thyroid hormone, hydrocortisone, and ADH, but not GH. After the initial operation, BMI increased rapidly in 4 patients. One patient had a height_Z increment of 0.59 within 0.8 years without GH treatment.

Seven patients (C07–C13, 31.8%) were diagnosed with NAFLD within 1–4.9 years post operation. One patient (C13)

received GH and all seven received thyroid hormone, hydrocortisone, and ADH. Of those patients (C07–C12) who did not receive GH treatment, 5 (83.3%) patients increased BMI_Z post operation by 1.92 (range 0.71–2.84). Only 1 patient (C08) showed decreased BMI_Z, but this patient was severely obese prior to the operation. Of these 6 patients, 4 (66.7%) showed catch-up growth (Fig. 3).

Nine patients (C14–C22, 40.9%) were diagnosed with NAFLD more than 5 years post operation, with average time interval 8.4±2.5 years. All were administered thyroid hormone, hydrocortisone, and ADH. Six of these patients received sex steroids and 4 patients received GH. Height_Z increased in 7 patients (C16–C22) regardless of GH treatment. Two of the 4 patients who received GH showed a decrease in BMI_Z.

Table 1. Clinical and biochemical characteristics of nonalcoholic fatty liver disease patients with childhood onset craniopharyngioma

		Preoprative					At diagnosis of nonalcoholic liver disease						
No.	Sex	Age (yr)	Height z score	BMI (z score)	IGF-1 (ng/mL)	Surgical approach	Time interval (yr)	Height z score	BMI (z score)	IGF-1 (ng/mL)	GH replacement/duration(yr)		Sex hormone replacement
C01	F	12.7	-1.39	22.0 (0.94)	62	TSA	0.0	-1.39	22.0 (0.94)	62	No (OP within 1 year)	-	-
C02	M	14.3	-1.94	18.3 (-0.75)	45	Craniotomy	0.0	-1.94	18.3 (-0.75)	45	No (OP within 1 year)	-	-
C03	M	10.1	-0.98	18.6 (0.26)	<10	Craniotomy	0.0	-0.98	19.8 (0.63)	<10	No (OP within 1 year)	-	-
C04	M	10.9	-2.82	19.6 (0.37)	238	Craniotomy	0.1	-2.82	22.2 (1.08)	54	No (OP within 1 year)	-	-
C05	F	11.0	-0.80	24.2 (1.8)	<10	Craniotomy	0.2	-0.88	26.0 (2.11)	<10	No (OP within 1 year)	-	-
C06	M	8.7	-2.08	17.3 (0.1)	51	TSA	0.8	-1.49	20.5 (0.98)	51	No (recurrence)	-	-
C07	M	13.6	-0.42	19.3 (-0.23)	474	TSA	1.1	-1.27	22.2 (0.49)	82	No (RT within 1 year)	-	-
C08	M	9.5	-0.75	26.0 (2.13)	63	Craniotomy	1.6	-0.78	26.3 (1.86)	67	No (good GV)	-	-
C09	F	12.5	-0.45	14.7 (-1.96)	-	Craniotomy	2.2	0.26	22.8 (0.88)	73	No (recurrence)	1.25	-
C10	F	7.4	-2.31	18.8 (1.27)	-	Craniotomy	2.5	-0.11	26.6 (2.46)	<10	No (imbalance)	0.31	-
C11	M	8.2	-1.41	15.0 (-0.97)	101	Craniotomy	2.6	-0.80	23.3 (1.34)	79	No (recurrence)	-	-
C12	F	5.8	-1.79	16.3 (0.53)	<10	Craniotomy	2.9	0.90	29.0 (3.09)	31	No (recurrence)	-	-
C13	M	2.8	-	-	-	Craniotomy	3.6	-2.11	16.7 (0.43)	371	Yes	*	-

C14	M	8.5	-	-	-	Craniotomy	5.3	-0.90	27.8 (1.75)	53	No (recurrence)	-	-
C15	M	10.0	-	-	-	Craniotomy	5.4	-2.00	25.4 (1.2)	45	No (recurrence)	1.54	-
C16	M	6.4	0.43	19.6 (1.63)	<10	Craniotomy	6.3	1.80	26.9 (1.72)	30	No (recurrence)	1.44	-
C17	M	7.0	-2.48	19.8 (1.49)	-	Craniotomy	7.8	0.87	35.8 (2.76)	86	No (refusal)	5.37	-
C18	F	5.8	-0.80	19.4 (1.92)	-	Craniotomy	8.4	0.77	19.0 (-0.3)	52	Yes	0.37	T-E 50 mg
C19	F	5.9	-0.40	18.7 (1.69)	-	TSA	8.9	0.92	24.1 (1.22)	17	No (recurrence)	-	E-V 2 mg, MP 5 mg
C20	F	8.0	-0.34	24.4 (2.54)	-	Craniotomy	10.1	2.34	23.7 (0.94)	124	Yes (intermittent use)	3.32	E-V 1 mg, MP 5 mg
C21	M	11.0	-0.59	27.0 (2.02)	133	Craniotomy	11.4	0.08	39.4 (3.18)	158	Yes	6.49	E-V 2 mg, MP 5 mg
C22	F	10.3	-0.91	23.5 (1.81)	-	Craniotomy	12.2	0.63	27.9 (2.05)	24	Yes (poor compliance)	7.49	T-U 1000 mg

BMI, body mass index; IGF−I, insulin−like growth factor−I; TSA, trans−sphenoidal approach; T−E, testosterone enanthate; E−V, estradiol valerate; MP, medroxyprogesterone; IM, intramuscular injection; T−U, testosterone undecanoate,
* Duration of GH replacement is not known due to outside treatment.

Liver enzyme and biochemical profiles at diagnosis of NAFLD

All 22 patients diagnosed with NAFLD (100%) had elevation of either AST or ALT over the normal range (40 IU/L) before they were diagnosed with NAFLD. ALT ≥ 60 IU/L was observed in 15 patients and AST ≥ 60 was found in 17 patients. An ALT/AST ratio > 1 was observed in 14 patients. Lipid profiles were measured in 13 patients (Table 2).

Hypertriglyceridemia was found in 9 patients and hypo-HDL (< 40 mg/dL) was observed in 7 patients. Homeostasis model assessment-insulin resistance (HOMA-IR) levels greater than the mean level for normal South Korean adolescents[17] were observed in 9 of 12 patients. Impaired fasting glucose was observed in 4 patients. Hyperuricemia (uric acid ≥ 7 mg/dL) was seen in nine patients.

GH treatment

Only five patients (C13, C18, C20-C22) were administered GH at NAFLD diagnosis (Table 1). The reasons for not administering GH for the other 17 patients included actual or risk of tumor recurrence (n=8, 47.1%), within a year post surgery or radiation therapy (n=6, 35.3%), or other cause

(body imbalance, refusal, normal growth velocity). IGF-I level < 3rd percentile was observed in 19 patients (Table 1). Two adults (C20, C21) with IGF-I > 100 ng/mL had received GH treatment but developed NAFLD more than 10 years after the initial operation.

Table 2. Metabolic profiles of nonalcoholic fatty liver disease patients with childhood onset craniopharyngioma

No.	AST/ALT (IU/L)	Chol/TG/LDL/HDL (mg/dL)	FBS (mg/dL)	Insulin (uIU/mL)	HOMA IR	UA (mg/dL)
C01	124/144	177/152/118/49	85	-	-	7.7
C02	63/90	187/-/-/-	109	9.2	2.1	3.9
C03	371/423	294/-/-/-	87	-	-	3.1
C04	118/187	153/73/93/47	83	8.3	1.7	3.8
C05	95/127	172/-/-/-	98	-	-	6.5
C06	61/56	219/264/138/33	94	-	-	7.8
C07	45/140	184/175/110/36	96	8.0	1.9	11.2
C08	79/33	163/-/-/-	97	-	-	6.7
C09	217/153	160/-/-/-	87	17.7	4.0	6.6
C10	54/48	143/368/50/20	91	-	-	9.9
C11	60/120	234/404/85/37	99	17.7	4.2	5.0
C12	55/62	117/-/-/-	91	-	-	6.5
C13	83/94	124/-/-/-	102	-	-	3.9
C14	40/40	141/97/81/40	91	43.9	9.9	6.2
C15	64/108	203/202/132/41	84	14.5	3.4	8.0

C16	73/121	125/171/76/34	89	42.8	9.4	6.0
C17	125/42	189/118/119/46	88	15.3	3.3	7.3
C18	61/37	140/92/86/40	124	18.8	5.8	9.3
C19	108/142	197/231/163/26	76	16.8	3.2	5.4
C20	45/41	195/-/-/-	102	-	-	4.5
C21	64/93	163/-/-/-	90	-	-	10.6
C22	75/96	176/260/86/38	89	16.9	3.7-	7.1

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Chol, cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment-insulin resistance; UA, uric acid

Discussion

Previous meta-analysis has shown the prevalence of NAFLD for obese children was 34.2%[18], and NAFLD was more common in co-craniopharyngioma with prevalence 46.8% in co-craniopharyngioma and especially 68.8% in co-craniopharyngioma with liver aminotransferase ≥ 40 IU/L. NAFLD may develop even within a year post craniopharyngioma surgery.

Genetics, epigenetics, environmental factors, insulin resistance, and obesity all influence fat accumulation in the liver. The fatty liver is then predisposed to oxidative stress, mitochondrial dysfunction, proinflammatory cytokine imbalances, and stellate cell activation, which lead to necro-inflammation and fibrosis[19]. Obesity is the main risk factor for pediatric NAFLD, with insulin resistance, hyperglycemia, and dyslipidemia also strongly associated with NAFLD.

While increasing survival of co-craniopharyngioma patients, hypothalamic obesity may predispose to NAFLD, metabolic syndrome, and poor quality of life[12-14,17]. Few studies have focused on NAFLD in craniopharyngioma[7]. Therefore, we reviewed the clinical characteristics of NAFLD in co-craniopharyngioma patients.

In the study, we used ALT or AST ≥ 40 IU/L as a cut-off for imaging studies. This level exceeds normal South Korean adolescent levels, for whom the normal AST level (IU/L) is 21.4±6.3 (boys) and 19.0±5.0 (girls), and the normal ALT level (IU/L) is 15.4±6.3 (boys) and 12.7±5.2 (girls)[20]. High serum ALT within the normal range increases the risk of all components of metabolic syndrome. In this study, two patients (C08, C18) with NAFLD showed ALT levels 33 and 37 IU/L, AST levels 79 and 61 IU/L, respectively. Generally, it is known that initial NAFLD state correlates better with elevated ALT than AST. However, ALT under 40 IU/L does not exclude the possibility of NAFLD[21]. ALT or AST may be within the normal range in co-craniopharyngioma with NAFLD[7].

Given the progressive nature of hypothalamic obesity, inadequate GH replacement, hypogonadism in co-craniopharyngioma, and the invasiveness of a liver biopsy, the exact prevalence of NAFLD and particularly NASH in co-craniopharyngioma is unclear. In this study, we observed ALT or AST elevation ≥ 40 IU/L in approximately 68% of co-craniopharyngioma patients. CT or sonographic findings typical of NAFLD were also observed in 68% of the cases that underwent imaging studies. This result is consistent with a recently published study that showed NAFLD occurred in approximately 50% of co-craniopharyngioma patients with

hypothalamic involvement more than 5 years after the craniopharyngioma diagnosis[7]. In the United States, liver transplants attributed to NAFLD-related liver disease increased from 1.2% in 2001 to 9.7% by 2009. The recipients were older, more likely to be female, and had higher BMI[22]. While simple steatosis carries a minimal risk of cirrhosis and liver failure in adults, NAFLD appears to follow a more aggressive course in pediatric cases than adults with NAFLD[23-26]. The natural course of NAFLD in patients with hypothalamic and pituitary dysfunction may be more aggressive than in the general population. Adams et al, reported that NAFLD developed relatively quickly (average 6.4 years) in 21 patients with pituitary/hypothalamic dysfunction (age range 9–78 years) and liver disease in these patients was severe: 60% of 10 patients who underwent biopsies had cirrhosis, and 14.3% of 18 NAFLD patients were either transplanted or died during follow-up[27]. That study included nine patients whose age at the time of developing hypothalamic/pituitary disease was < 18 years.

Craniopharyngiomas have many features that can affect the development or aggravation of NAFLD independently or synergistically. Weight gain occurs before the diagnosis, progresses rapidly during the first 6–12 months after treatment, and results in severe obesity in half of the patients[1]. Our study

showed that NAFLD could develop very early, even at craniopharyngioma diagnosis, and NAFLD patients gained more weight during this period. Obesity in these children is related to hypothalamic dysfunction, resulting in disrupted or impaired sensitivity to feeding-related signals involving leptin, insulin, and ghrelin, and reductions in the basal metabolic rate, sleep disturbance, and physical inactivity[3,4,28]. Children with craniopharyngioma and hypothalamic obesity have more features of metabolic syndrome and insulin resistance than BMI-matched controls[29,30]. NAFLD was observed in 50% of co-craniopharyngioma patients, who tend to have more severe insulin resistance[31]. The relationship between NAFLD and metabolic syndrome is bidirectional, in that NAFLD can predispose to metabolic syndrome features, which can, in turn, exacerbate NAFLD or increase development risk in those without a pre-existing diagnosis[32].

In our study, dyslipidemia was observed in some NAFLD patients, but dyslipidemia or hyperuricemia are insufficient predictors for NAFLD. NAFLD is related to endocrine diseases such as hypogonadism, hypothyroidism, growth hormone deficiency, and hypercortisolism[11]. NAFLD is more prevalent in hypopituitarism patients than control subjects, and severe GH deficiency predisposes to a serious degree of hepatic steatosis in NAFLD[33]. For 17 (77.3%) of 22 patients, no GH was

administered before NAFLD diagnosis. The effect of GH replacement is controversial. In adults with GH deficiency, GH replacement improves the serum liver enzyme levels, and it is important to avoid body weight gain to optimize this effect[34]. It is not clear whether GH replacement improves NAFLD associated with co-craniopharyngioma. Although GH therapy induced excellent linear growth in co-craniopharyngioma patients, it failed to ameliorate the hypothalamic obesity[14,35]. Our study showed that NAFLD course, based on ALT or AST, ranged from improvement to waxing and waning or to persistent, regardless of GH replacement during follow-up. We suggest that patients who recover from NAFLD or have normal liver function have an enhanced lifetime chance of developing NAFLD because risk factors such as obesity, inactivity, sleep disturbance, and metabolic syndrome may worsen at any time. However, it would be inappropriate to compare the 22 patients with NAFLD and 13 patients without NAFLD who had imaging studies, because the studies were not performed at regular periods due to the retrospective study. This is one of the study limitations, which should be considered when planning follow-up studies.

It is pointless that comparing 22 patients with NAFLD and 13 patients without NAFLD who did imaging studies, because imaging studies were not done at regular period of time due to

retrospective study setting. That is one of the limitations of this study and looking forward next prospective study setting.

IGF-I directly modulates the expression of acute phase reactants. Decreasing C-reactive protein and fibrinogen levels and circulating IGF-I levels showed inverse correlations with NAFLD fibrosis score and inflammatory biomarkers[36]. An IGF-I level < 3rd percentile was observed in 19 NAFLD patients in our study. Although the IGF-I level was low, some patients showed catch-up height growth at NAFLD diagnosis. This normal growth despite GH deficiency may be explained by a complex series of metabolic events, including obesity induced hyperinsulinism[1]. Normal growth does not guarantee that IGF-I level is sufficient to prevent NAFLD.

Preoperative and postoperative hypothalamic damage may contribute to postoperative weight gain[14] and poor quality of life[1]. The current study showed that most cases had surgeries through craniotomy rather than trans-sphenoidal approach (TSA), although TSA was used in some patients with favorable tumor location since 2010. We did not review the degree of hypothalamic damage, which is another limitation of the study.

There is no proven, safe, effective treatment for NAFLD[18,37] or hypothalamic obesity[5] in children. Although lifestyle modification can improve NAFLD in many children[18,37], lifestyle intervention is useless in hypothalamic obesity[5]. To improve

quality of life and metabolic condition, treatment should focus on preserving hypothalamic function and optimizing lifestyle, including adherence to medical therapy, nutrition, physical activity, sleeping, social skills, and mental wellbeing.

This retrospective study had some limitations. First, we could not routinely check biochemical parameters (liver enzyme, lipid, glucose, and insulin), lifestyle (diet, physical activity, and daytime somnolence), total or visceral body fat, and imaging studies for all patients. Second, ultrasonography was not performed for some patients with ALT or AST elevation $\geq$ 40 IU/L. Third, NAFLD could have been missed in some co-craniopharyngioma patients with ALT or AST < 40 IU/L in these clinical settings.

In conclusion, NAFLD is common in co-craniopharyngioma survivors, and may develop earlier than in simple obesity. If ALT or AST is elevated above 40 IU/L, the child should undergo noninvasive examinations, including ultrasonography, serum biomarkers, and transient elastography. All patients should receive intensive, individualized lifestyle interventions as soon as possible to decrease risk of progressive obesity, metabolic syndrome, and NAFLD.

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국문초록

소아기에 발생한 두개인두종 환자에서 치료 후 비알코올성 지방간 발생에 관한 연구

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목적: 소아기에 발생한 두개인두종 환자들에게 뇌하수체성 비만은 비알코올성 지방간을 유발시키기 쉽다. 이 논문에서는 소아기에 발생한 두개인두종 환자들에서 치료 후 발생하는 비알코올성 지방간의 특성을 연구하고자 하였다.

방법: 본 연구에서는 2000 년도부터 2016 년도 동안 15 세 이하에서 두개인두종에 대한 첫 번째 수술을 받았던 75 명의 환자들에 대하여 후향적으로 조사하였다.

결과: 소아기에 발생한 두개인두종 환자 75 명 중 AST 혹은 ALT 가 40 IU/L 이상으로 상승한 환자는 51 명이었다. 이 가운데 32 명의 환자에게 영상검사를 시행하였고, 22 명의 (남아 59%, 첫

번째 수술 이후 4.3±4.0 년에 발생) 환자가 비알코올성 지방간으로 진단되었다. 소아기에 발생한 두개인두종 환자 중 비알코올성 지방간의 추정된 발병률은 46.8% 였다. 두개인두종에 대한 첫 번째 수술시의 평균 연령은 9.1±2.9 세였다. 수술 이후 1 년 이내에 지방간으로 진단된 환자는 6 명 (27.3%) 이었다. 수술 당시의 초기 키와 체중 정보가 있는 19 명 환자들의 체질량지수 z 값의 평균은 1.37±1.01 (범위 −0.75 to 3.18) 이었는데, 이 가운데 4 명 (18.2%)이 과체중이었으며, 9 명 (40.9%)은 비만이었다. 수술시에 비하여 체질량지수 z 값이 비알코올성 지방간 진단 당시에 상승한 환자는 13 명(68.4%)였으며, 그 상승값은 평균 1.13 (범위 0.10−2.84) 였다. 비알코올성 지방간으로 진단된 시점에 성장 호르몬을 투약하지 않았던 환자는 17 명이었고, IGF−1 값이 3 백분위수 미만이었던 환자는 19 명이었다.

결론: 비알코올성 지방간은 소아기에 발생한 두개인두종 환자에게서 흔하며, 일찍 발생할 수 있다. ALT 나 AST 가 40 IU/L 이상이라면, 진단적 검사를 시행해야 한다.

주요어: 소아기 두개인두종, 비알코올성 지방간, 성장 호르몬 부족, 시상하부, 비만

학번: 2015−22259