Endocrinology, Diabetes & Metabolism CASE REPORTS

H Takahashi and others | NASH treated with GH

ID: 21-0148; March 2022
DOI: 10.1530/EDM-21-0148

A 17-year-old boy with lymphocytic infundibuloneurohypophysitis who developed non-alcoholic steatohepatitis effectively treated with growth hormone

Hidekuni Takahashi, Shigeo Nishimata, Atsushi Kumada, Gaku Yamanaka, Yasuyo Kashiwagi and **Hisashi Kawashima**

Department of Pediatrics and Adolescent Medicine, Tokyo Medical University, Tokyo, Japan

Correspondence should be addressed to H Kawashima
Email
hisashi@tokyo-med.ac.jp

Summary

We encountered a case of childhood-onset lymphocytic infundibuloneurohypophysitis, based on the MRI and endocrinological findings, with decreased function of the anterior and posterior lobes of the pituitary. Three years after the diagnosis, the patient developed non-alcoholic steatohepatitis (NASH), which was effectively treated by growth hormone (GH) supplementation. The present case demonstrated that NASH can be effectively treated by short-term GH supplementation, even in late childhood.

Learning points:

- In recent years, the efficacy of growth hormone replacement therapy in normalizing the liver function of adult-onset growth hormone deficiency patients with non-alcoholic steatohepatitis (NASH) has been reported.
- Lymphocytic infundibuloneurohypophysitis is a very rare disease, particularly in childhood.
- We here presented a rare case of a child with lymphocytic infundibuloneurohypophysitis who developed NASH and showed substantial improvement in liver function after growth hormone treatment.

Background

Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) has been attracting attention as a complication of adult-onset growth hormone deficiency (AGHD). Previous studies demonstrated that the actions of growth hormone (GH) and signaling in hepatocytes play important roles in the lipid metabolism of hepatocytes and the prevention of fatty liver development. In recent years, the efficacy of GH replacement therapy in normalizing the liver function of AGHD patients with NAFLD/NASH has been reported (1). However, the efficacy of GH administration in pediatric patients with pituitary dysfunction who develop NAFLD/NASH remains unknown. We here presented a case of a patient with lymphocytic infundibuloneurohypophysitis who developed NASH and showed a substantial improvement in hepatic dysfuction after GH treatment.

Case presentation

A 14-year-old boy was admitted to our department because of polydipsia and polyuria. His past history was unremarkable. From 13 years and 3 months of age, he drank more than 20 L of water a day and complained of constant polyuria as well as weight loss (12 kg loss in a year). At the same time, he experienced emotional instability, flushing, vertigo, palpitations, and lower limb pain and

ID: 21-0148; March 2022
DOI: 10.1530/EDM-21-0148

was often absent from school. At the age of 14 years and 3 months, he was admitted to our hospital for a detailed examination. On admission, his height was 165 cm (+0.1 S.D.) with normal height velocity, and his weight was 68 kg (+1.3 S.D.). He had no armpit hair. His external genitalia had a male appearance. Testicular capacity was 4 mL each, and penis length was 3 cm (Tanner classification 3). Ophthalmological examination demonstrated no obvious abnormalities in visual acuity, eye movements, or visual field. His father had diabetes and rheumatoid arthritis.

His complete blood count (CBC) was normal. His total bilirubin level was 0.9 mg/dL, and his kidney function was normal. His C-reactive protein (CRP) was less than 0.05 mg/dL, and his IgG and IgG4 levels were 1350 and 14.1 (normal range: 11–121) mg/dL, respectively. Lumbar puncture showed no abnormalities. Total urine volume was 25.4 L per day. Serum and urinary osmolality were 285 and 101 mOsm/L, respectively. His ADH level was low at 0.5 (normal range: < 2.8) pg/mL. Cortisol and adrenocorticotrophic hormone (ACTH) levels were normal. GH was 0.18 (normal range: 0.13–9.8) ng/mL. Insulin-like growth factor binding protein-3 (IGFBP-3) and IGF-1 levels were normal, at 2.71 (normal range: 2.55–4.59) mg/mL and 251 (normal range: 142–540) ng/mL, respectively. thyroid-stimulating hormone (TSH) was 1.81 (normal range: 0.61–4.23) μU/mL, luteinizing hormone (LH) was 2.42 (normal range: 0.79–5.72) MIU/mL, and follicle-stimulating hormone (FSH) was 2.31 (normal range: 2.00–8.30) MIU/mL. human chorionic gonadotrophin (HCG) and HCG-β were both less than detectable levels. Prolactin was borderline high at 13.72 (normal range: 3.6–12.8) ng/mL. Free thyroxine and free tri-iodothyronine levels were 1.18 and 3.12 pg/mL, respectively, which were both within the normal range. The level of testosterone was prepubertal as 0.16 ng/mL. His laboratory data were shown in Table 1. Anti-nuclear antibodies and anti-pituitary antibodies were negative. His karyotype was 46,XY. Pituitary function tests using a simultaneous 4-drug load (growth hormone-releasing peptide (Pralmorelin Hydrochloride), corticotrophin-releasing hormone (CRH), thyrotrophin-releasing hormone (TRH), and LH-RH) showed normal responses to GH, ACTH, cortisol, and TSH. LH and FSH showed a low response and prolactin showed an over-response. The HCG challenge test showed a normal response. His urine osmolality did not change during the water deprivation test but was improved by Pitressin administration.

T1 weighted image head MRI displayed a loss of high signal in the posterior pituitary and a mass in the infundibulum. MRI with gadolinium contrast displayed uniform effect in the mass and the pituitary body. Transcranial biopsy showed chronic inflammatory granulation tissue with infiltration of $CD3^+$ $CD20^+$ lymphocytes but neither IgG4-positive plasma cells nor neoplastic lesions. From these findings, the patient was diagnosed as having lymphocytic infundibuloneurohypophysitis, central diabetes insipidus, and secondary hypogonadism. He was given hormone replacement treatments of desmopressin (DDAVP), FSH, and hCG. Glucocorticoid was not administered as its therapeutic effects remain controversial and also because the patient was in his growth period. No enlargement of

Table 1 Laboratory findings of the patient.

	Normal range	Age	
		14 years	17 years
BS (mg/dL)	70-109	106	108
TP (g/dL)	6.6–8.1	7.6	8.3
ALB (g/dL)	4.1–5.1	4.8	4.6
AST (IU/L)	<30	16	155
ALT (IU/L)	<30	12	268
BUN (mg/dL)	8.0–20	11.2	15.0
Cr (mg/dL)	0.65–1.07	0.62	0.66
LDH (IU/L)	124–222	210	343
γ-GTP (IU/L)	13–64	N.D.	74
T-bil (mg/dL)	0.4–1.5	0.9	0.9
Na (mEq/L)	138–145	143	138
K (mEq/L)	3.6–4.8	4.1	4.3
Cl (mEq/L)	101–108	110	103
CRP (mg/dL)	<0.3	0.05	1.05
IgG (mg/dL)	870–1700	1,350	1,450
IgA (mg/dL)	110–410	142	132
IgM (mg/dL)	31–200	60	80
HbA1c (%)	4.3–5.8	4.9	5.4
CPR (ng/m)	0.8–2.5	3	3
T-cho (mg/dL)	<220	175	222
LDL (mg/dL)	<140	53.7	158
HDL (mg/dL)	>40	57	31
ANA (X)	<40	< 40	320
Anti-pituitary Ab	(–)	(–)	(–)
Serum osmotic pressure (mOsm/L)	275–290	285	N.D.
Urine osmotic pressure (mOsm/L)	50–1300	101	N.D.
GH (ng/mL)	0.13–9.8	0.18	N.D.
TSH (μU/mL)	0.61–4.23	1.81	N.D.
IGFBP-3 (μg/mL)	2.55–4.59	2.71	3.14
IGF-1 (ng/mL)	142–540	251	114
LH (MIU/mL)	0.79–5.72	2.42	0.6
FSH (MIU/mL)	2.00–8.30	2.31	0.36
PRL (ng/mL)	4.29–13.69	13.72	N.D.
Cortisol (μg/mL)	4.0–18.3	21.2	10.4
ACTH (pg/mL)	7.2–63.3	31.5	23.5
ADH (pg/mL)	<2.8	0.5	0.8
HCG	<1.0	< 1.0	N.D.
HCG-β	<0.1	< 0.1	N.D.
teststerone (ng/mL)	1.31–8.71*	0.16	5.44

*Normal range of adult.
N.D., not determined.

ID: 21-0148; March 2022
DOI: 10.1530/EDM-21-0148

the tumor was detected on MRI performed 1 year after the start of treatment. His ACTH, TSH, and testosterone levels were periodically measured during the treatment period by CRH, TRH, and hCG stimulation tests and no abnormalities were observed. Hormone replacement treatments except for DDAVP were ended after 2 years because of sexual maturation.

At the age of 17 years (1 year after hormone replacement was ended), weight gain (+28 kg in about 2 years), obesity, and increases in aspartate transaminase (AST) and alanine transaminase (ALT) levels were observed, CRP became persistently weakly positive, and ANA became positive. No obvious cause could be identified for his obesity, such as orthopedic injury, changes in nonendocrine medications, a change from attending school to a sedentary profession, etc. Repeated hormone stimulation tests demonstrated normal responses. Abdominal echocardiography displayed a bright liver and increased contrast liver/kidney density. Liver biopsy showed fatty liver with prominent large droplets as well as small droplets (total about 30%). There were no necrotic regions or infiltration of fibrosis. There was no inflammation in Glisson's capsule, and the pathology was compatible with NASH.

Although FSH and hCG therapy were restarted, there was no improvement in the patient's liver function. Therefore, GH replacement therapy was started following FSH and hCG therapy, and his abnormal liver function immediately improved. His secondary sexual characteristics gradually developed, and at the age of 18, ejaculation was confirmed (Fig.1).

Discussion

In recent years, NAFLD/NASH has been attracting attention as a complication of AGHD. Mouse models of GH deficient in hepatocyte-specific GH receptor, JAK2, and STAT5 deletion have been shown to develop fatty liver (2). These data demonstrate that GH actions and GH signaling in hepatocytes play important roles in the lipid metabolism of hepatocytes and the prevention of fatty liver development.

Takahashi *et al.* previously reported the efficacy of GH replacement therapy in patients with NAFLD/NASH. In the AGHD group, 77% were diagnosed with NAFLD by echocardiography. Liver biopsy was performed in 16 patients, and 14 of them were pathologically diagnosed as having NASH, showing lipid droplet deposition and evidence of inflammation and fibrosis. GH replacement therapy was performed in the AGHD patients, and liver function was significantly decreased by 6 months of treatment, and levels of hyaluronic acid and type 4 collagen, which are markers of fibrosis, were decreased after 1 year of treatment. At least 21% of all AGHD patients analyzed had NASH. Therefore, NAFLD/NASH can be prevented or ameliorated by administering GH in pediatric patients with pituitary dysfunction, as shown previously as well as in the present case (1).

In the present case, the patient had childhood-onset lymphocytic infundibuloneurohypophysitis and developed NASH after 3 years. Lymphocytic autoimmune hypophysitis is a rare chronic inflammatory disease

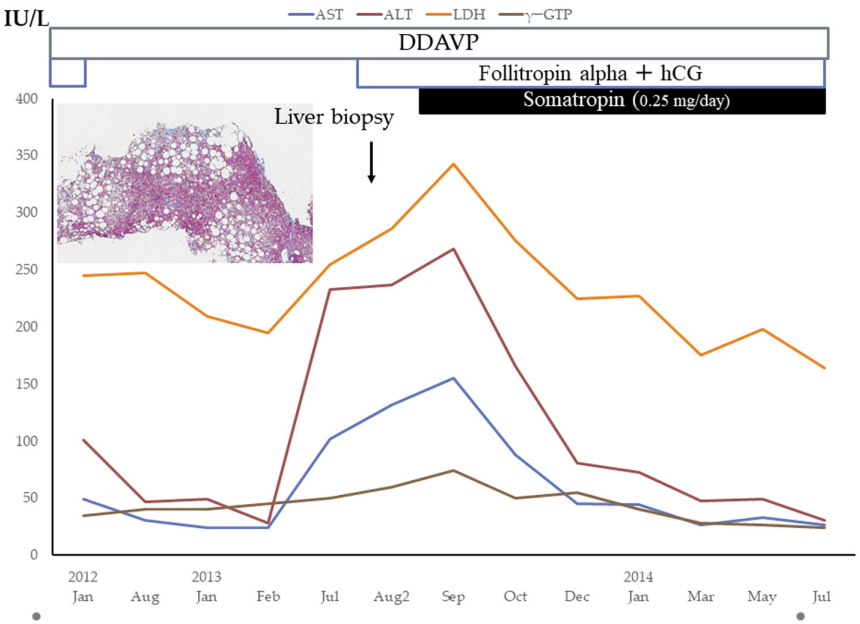

Figure 1
Liver pathology and fluctuation of hepatobiliary enzyme levels in the patient after the introduction of growth hormone therapy. (Liver biopsy showed clear fatty liver pathology, which was compatible with NASH. After starting GH therapy, liver function tests immediately improved.)

ID: 21-0148; March 2022
DOI: 10.1530/EDM-21-0148

showing inflammation in the hypothalamus and pituitary gland, accompanied by autoimmune cell infiltration of mainly lymphocytes, resulting in decreased pituitary function (3, 4). The cause of this disease remains unknown to date, and it is a rare disease designated as an intractable disease. The prevalence of this disease in Europe and the United States is 1 in 9 million, and a majority of the cases have been reported from Japan (2010 Japan/World report: 130/379 cases). It is classified into either anterior or posterior lobitis (pituitary infundibulum neuritis) depending on the onset site. Most patients require permanent replacement of one or more hormones. For anterior hypophysitis, there is no established treatment because remission is usually achieved with pituitary biopsy, and rarely spontaneous remission is observed.

The present patient was not hyperphagic when he developed obesity. There may have been suprasellar involvement of his lymphocytic hypophysitis (causing hypothalamitis), which may have altered the energy expenditure/intake centers of the hypothalamus, leading to hypothalamic obesity. The present patient demonstrated partial dysfunction of the anterior pituitary gland in addition to the posterior pituitary gland at the age of 14 years. Although his GH secretion and IGF-1 were normal, he developed NASH, which was effectively treated by GH replacement therapy. Lymphocytic infundibuloneurohypophysitis is a very rare disease, particularly in childhood (5). We have listed the cases reported to date in Table 2 (6, 7). Patients of both sexes have been observed among children of various ages. Some patients showed self-limited disease and symptoms and MRI findings of spontaneous regression. Therefore, he was suspected to have silent dysfunction of GH from the time of disease onset. Nakajima *et al.* reported a similar case of a child who developed NASH and craniopharyngioma (8).

Alternatively, the patient experienced weight gain and developed obesity, which may result in secondary GH deficiency. Liang *et al.* reported that GH secretion is reduced in obese children with NAFLD (9). A crucial problem of hypophysitis is that pediatric medical insurance differs depending on the local government, and treatment may be interrupted when switching from pediatric medical insurance to adult medical insurance. At present, an effective treatment for NAFLD that can improve a patient's long-term prognosis has not been established. Therefore, elucidation of the pathogenic mechanism of NASH in AGHD may deepen our understanding of the general pathological condition of patients with NASH and may contribute to the development of effective therapies.

Table 2 Reported pediatric cases of lymphocytic infundibuloneurohypophysitis.

Case number	Age of onset	Sex	CC	Method of diagnosis	MRI	Anterior pituitary function	Treatment	Outcome*	NAFLD/NASH	Reference
1	2	Male	Diabetes insipidus	Not described	+		PSL 2mg/kg	+/–	–	Momoi *et al.* (6)
2	8	Female	Diabetes insipidus	Transcranial sur. Histopathology	+	Growth hormone deficiency	GC pulses (30 mg/kg) 3 days DDAVP	+/+	–	Maghnie *et al.* (5)
3	13	Male	Diabetes insipidus	Histopathology	+			–/–	–	Terao *et al.* (7)
4	13	Male	Diabetes insipidus	Histopathology	+	Partially deficient	hCG	–/–	+	Our case

*Improvement of MRI/disappearance of diabetes insipidus.

ID: 21-0148; March 2022
DOI: 10.1530/EDM-21-0148

This is the youngest report to our knowledge on GH treatment for NASH in a patient with childhood-onset lymphocytic infundibuloneurohypophysitis. Although the patient's GH secretion both with/without loading was normal, NASH occurred in his disease course, and supplementation of GH was effective for treating his liver dysfunction.

Declaration of interest

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

Funding

This work was supported in part by a Grant-in Aid from the Japan Agency for Medical Research and Development (grant number: 20fk0108058h0003). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (SH3841).

Patient consent

We obtained written informed consent from the patient and from his parent about the presentation including the publication with proper consideration for his personal information.

Author contribution statement

H T and H K designed the study; S N, A K, and Y K performed experiments; and H T wrote the manuscript; G Y gave technical support and conceptual advice. All authors read and approved the final manuscript. H K critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

References

1 Takahashi Y, Iida K, Takahashi K, Yoshioka S, Fukuoka H, Takeno R, Imanaka M, Nishizawa H, Takahashi M, Seo Y, *et al.* Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency. *Gastroenterology* 2007 **132** 938–943. (https://doi.org/10.1053/j.gastro.2006.12.024)

2 Kaltenecker D, Themanns M, Mueller KM, Spirk K, Suske T, Merkel O, Kenner L, Luís A, Kozlov A, Haybaeck J, *et al.* Hepatic growth hormone – JAK2 – STAT5 signalling: metabolic function, non-alcoholic fatty liver disease and hepatocellular carcinoma progression. *Cytokine* 2019 **124** 154569. (https://doi.org/10.1016/j.cyto.2018.10.010)

3 Imura H, Nakao K, Shimatsu A, Ogawa Y, Sando T, Fujisawa I & Yamabe H. Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. *New England Journal of Medicine* 1993 **329** 683–689. (https://doi.org/10.1056/NEJM199309023291002)

4 Caturegli P, Lupi I, Landek-Salgado M, Kimura H & Rose NR. Pituitary autoimmunity: 30 years later. *Autoimmunity Reviews* 2008 **7** 631–637. (https://doi.org/10.1016/j.autrev.2008.04.016)

5 Maghnie M, Genovese E, Sommaruga MG, Aricò M, Locatelli D, Arbustini E, Pezzotta S & Severi F. Evolution of childhood central diabetes insipidus into panhypopituitarism with a large hypothalamic mass: is 'lymphocytic infundibuloneurohypophysitis' in children a different entity? *European Journal of Endocrinology* 1998 **139** 635–640. (https://doi.org/10.1530/eje.0.1390635)

6 Momoi R, Hiramatsu H, Okumura M, Yoshida N, Tanaka R, Fujisawa I, UematsuA, MuroiJ, KawaiM, YorifujT, *et al.* A 6 year-old boy with suspected lymphocytic infundibuloneurohypophysitis (LIN) for 4 years following. *Horumon and Rinsho* 1998 **46** (Supplement) 78–82. [Article in Japanese].

7 Terao T, Taya K, Sawauchi S, Nakazaki H, Numoto RT, Yamaguchi Y, Murakami S, Abe T & Hashimoto T. Two cases of lymphocytic infundibuloneurohypophysitis. *No Shinkei Geka* 2003 **31** 1229–1235. [Article in Japanese].

8 Nakajima K, Hashimoto E, Kaneda H, Tokushige K, Shiratori K, Hizuka N & Takano K. Pediatric nonalcoholic steatohepatitis associated with hypopituitarism. *Journal of Gastroenterology* 2005 **40** 312–315. (https://doi.org/10.1007/s00535-004-1541-4)

9 Liang S, Yu Z, Song X, Wang Y, Li M & Xue J. Reduced growth hormone secretion is associated with nonalcoholic fatty liver disease in obese children. *Hormone and Metabolic Research* 2018 **50** 250–256. (https://doi.org/10.1055/s-0043-124970)

Received in final form 12 February 2022
Accepted 21 February 2022