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Clinical case seminar — familial intracranial germinoma

Opis przypadku — występujący rodzinnie wewnątrzczaszkowo *germinoma*

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Abstract

Background: Intracranial germinomas (ICG) are uncommon brain neoplasms with extremely rare familial occurrence. Because ICG invades the hypothalamus and/or pituitary, endocrine dysfunction is one of the common determinants of these tumours.
We present two brothers with a history of ICG. Patient 1 is a 25-year-old male who suffered from weakness of the right half of his body at the age of 18 years. Cranial MRI revealed a mass lesion in the left thalamus. He underwent neurosurgery, and the tumour was removed completely. Histopathological (HP) and immunohistochemical analyses verified the diagnosis of pure germinoma. He experienced complete remission of the tumour after radiation therapy. At the age of 22 years a diagnosis of isolated growth hormone deficiency (IGHD) was established and GH replacement was initiated. Molecular genetic analysis of the tumour tissue detected the mutation within exon 2 in *KRAS* gene. Patient 2 is a 20-year-old man who presented with diabetes insipidus at the age of 12 years. MRI detected tumour in the third ventricle and pineal region. After endoscopic tumour biopsy the HP diagnosis was pure germinoma. He received chemotherapy followed by radiotherapy and was treated with GH during childhood. At the age of 18 years GH replacement was reintroduced. A six-month follow-up during the subsequent two years in both brothers demonstrated the IGF1 normalisation with no MRI signs of tumour recurrence.
Conclusion: To the best of our knowledge, so far only six reports have been published related to familial ICG. The presented two brothers are the first report of familial ICG case outside Japan. They have been treated successfully with GH therapy in adulthood. **(Endokrynol Pol 2018; 69 (5): 612–618)**

Key words: *intracranial germinoma, familial occurrence, hypopituitarism, GH replacement*

Streszczenie

Wstęp: Rozrodczaki wewnątrzczaszkowe (*intracranial germinomas*, ICG) to rzadkie nowotwory mózgu, a szczególnie rzadko stwierdza się ich występowanie rodzinne. W związku z tym, że ICG zajmuje podwzgórze i/lub przysadkę mózgową, zaburzenia endokrynologiczne są jednym z najczęstszych wyznaczników obecności tych guzów.
W pracy przedstawiono dwóch braci z ICG. Pacjent 1 to 25-letni mężczyzna, u którego w wieku 18 lat wystąpiło osłabienie mięśni po lewej stronie ciała. Badanie metodą rezonansu magnetycznego (MRI) czaszki ujawniło masę w lewym wzgórzu. Chorego poddano zabiegowi neurochirurgicznemu, podczas którego guz został całkowicie usunięty. Badania histopatologiczne i immunohistochemiczne potwierdziły rozpoznanie czystej postaci rozrodczaka. Po radioterapii nastąpiła całkowita remisja guza. W wieku 22 lat u chorego zdiagnozowano izolowany niedobór hormonu wzrostu (*isolated growth hormone deficiency*, IGHD) i wdrożono terapię zastępczą hormonem wzrostu (*growth hormone*, GH). Genetyczna analiza molekularna tkanki guza wykazała mutację w eksonie 2 w genie *KRAS*. Pacjent 2 to 20-letni mężczyzna, u którego w wieku 12 lat stwierdzono moczówkę prostą. W badaniu MRI wykryto guz w okolicy trzeciej komory i szyszynki. Po ocenie histopatologicznej materiału pobranego za pomocą biopsji endoskopowej postawiono diagnozę czystego rozrodczaka. U chorego zastosowano chemioterapię, a następnie radioterapię, a także podawano GH w okresie dzieciństwa. W wieku 18 lat u chorego wznowiono terapię GH. Sześciomiesięczna obserwacja obu braci w następnych 2 latach wykazała normalizację IGF1 przy braku objawów nawrotu guza w badaniu MRI.
Wnioski: Według najlepszej wiedzy autorów dotychczas opublikowano 6 doniesień na temat rodzinnego występowania ICG. Przedstawieni w niniejszej pracy bracia są pierwszym opisanym przypadkiem rodzinnego ICG poza Japonią. W okresie dorosłym chorzy są leczeni GH z dobrym skutkiem. **(Endokrynol Pol 2018; 69 (5): 612–618)**

Słowa kluczowe: *rozrodczak wewnątrzczaszkowy, występowanie rodzinne, niedoczynność przysadki, terapia zastępcza GH*

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Case report

Our patients are two brothers with history of intracranial germinomas (ICG). Their auxological and hormonal parameters are shown in Table I. They have a third brother, who is healthy. Their father died from malignant melanoma, while their grandfather had diabetes insipidus of unknown aetiology.

Patient 1 is a 25-year-old male who suffered numbness and weakness of the right side of the body for one month at age 18 years. Cranial MRI showed an expansive process that included part of the brain stem and the left thalamus (Figures 1A, B). He underwent neurosurgery, and the tumour was removed completely. According to histopathological (HP) and immunohistochemical analyses, a diagnosis of pure germinoma was established (Figures 2A–C). Severe neurological sequelae occurred after surgery: central facial nerve paresis, truncal ataxia, right-sided hemiparesis, and dysarthria. Radiotherapy was performed a month after surgery (total dose 51 Gy). He experienced complete remission of the tumour and remained recurrence-free for the next four years. At the age of 22 years he was investigated by a neuroendocrinologist, whereupon a physical examination revealed the abovementioned neurological manifestations and asthenic constitution. Bone mineral density (BMD) was severely decreased (Z score L1–L4 = –3.9), and quality of life (QoL) measured by AGHDA questionnaire (Adult GH Deficiency Assessment) was poor. GH replacement had started four years after the complete remission. The GH maintenance dose of 0.3 mg daily has been sufficient for the achievement of IGF1 normalisation. The two years of GH replacement therapy improved body composition and QoL, while BMD did not change (Table II). Cranial and spinal MRI showed no signs of tumour recurrence (Figures 1C, D). Genetic analysis of tumour tissues confirmed variant within exon 2 in KRAS gene (NM_033360.3, c.35G>A, p.G12V) (Figure 2E).

Table I. *Auxological and hormonal characteristics of patients*

Tabela I. *Auksjologiczna i hormonalna charakterystyka chorych*

	Patient 1	Patient 2
Age	25	20
Body height [cm]	176	176
Body weight [kg]	47	71
BMI [kg/m^2]	15.2	22.7
Hormones and tumour markers		
FT4 (7–18 ng/ml)	20.2	14.5
TSH (0.3–5.5 mU/l)	1.4	3.1
Cortisol (131–642 nmol/l)	354	432
FSH (2.5–15 mU/l)	5.3	1.8
LH (2.5–16 mU/l)	3.6	3.7
Testosterone (2.8–8.0 ng/ml)	5.8	3.6
Growth hormone (0–28.5 mU/l)	1.7	1.5
IGF1 [ng/ml] before GH therapy on GH therapy	 117 (116–358) 160	 195 (193–731) 370
PRL (121–545 mU/l)	670	411
ACTH (10–90 ng/l)	38	46
PTH (0–80 ng/l)	35	27
ß HCG (< 0.5 ng/ml)	0.178	0.295
αFP (< 5 ng/ml)	1.1	2.1
Glucagon test		
GH peak [mU/l]	1.8	8.3
Cortisol [nmol/l]	basal 310…… peak 710	basal 392…… peak 690
ITT-insulin tolerance test		
GH peak [mU/l]		6.0
Cortisol [nmol/l]		basal 270…… peak 499
PRL [mU/l]		basal 421….. peak 791

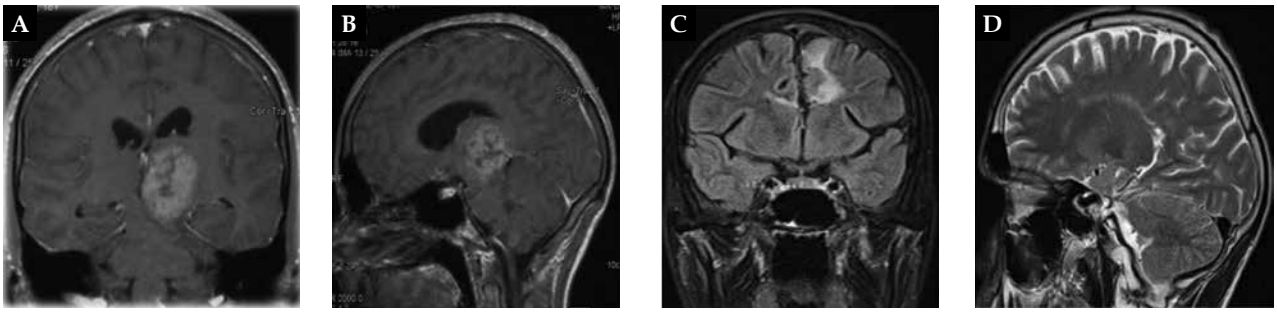

Figure 1A, B. *Preoperative MRI of Patient 1 shows tumour in the left thalamus;* **C, D.** *MRI of Patient 1, six years after radiotherapy and two years of GH replacement, shows no signs of tumour recurrence*

Rycina 1A, B.*Przedzabiegowe badanie MRI Pacjenta 1 pokazuje guz w lewym wzgórzu;* **C, D.** *Badanie MRI Pacjenta 1 wykonane sześć lat po radioterapii i dwa lata po rozpoczęciu terapii zastępczej GH. Nie ma żadnych cech nawrotu nowotworu*

Table II. *DXA measurement of bone mineral density (BMD) and body composition in both patients*

Tabela II. *Pomiar metodą DXA gęstości mineralnej kości (BMD, bone mineral density) i składu ciała u obu chorych*

DXA	Patient 1		Patient 2	
		Before GH 2yrs GH therapy		Before GH 2yrs GH therapy
Z sc L1-L4	–3.9	–3.8	–1.5	–2.2
Z sc femoral neck	–2.9	–3.2	–1.5	–1.4
% Fat	20.2	16.4	26	23.5
FM — fat mass [kg]	9.1	7.9	17.1	16.1
LBM — lean body mass [kg]	34.5	37.6	45.7	50.3
TBMC — total bone mineral content [kg]	1.5	1.5	2.1	2.1

Patient 2 is a 20-year-old man, the younger brother of Patient 1. At the age of 12 years he started to complain of excessive water intake. The diagnosis of diabetes insipidus was established and vasopressin therapy was started. Two months later, headaches, vomiting, and diplopia occurred, which indicated acute hydrocephalus. An MRI revealed a tumour in the third brain ventricle and pineal region, with hydrocephalus and dilatation of both lateral ventricle (Figure 3A, B). A neurosurgeon performed endoscopic ventriculocisternostomy and tumour biopsy. Histopathology diagnosis was the same as those seen in his brother's tumour — pure germinoma (Figure 2D). Immunohistochemistry and genotyping could not performed due to the lack of an available surgical specimen. The patient received chemotherapy followed by radiotherapy (total dose 55 Gy), after which MRI showed tumour disappearance. His paediatrician included GH replacement from 12 to 17 years of age. The patient achieved normal body

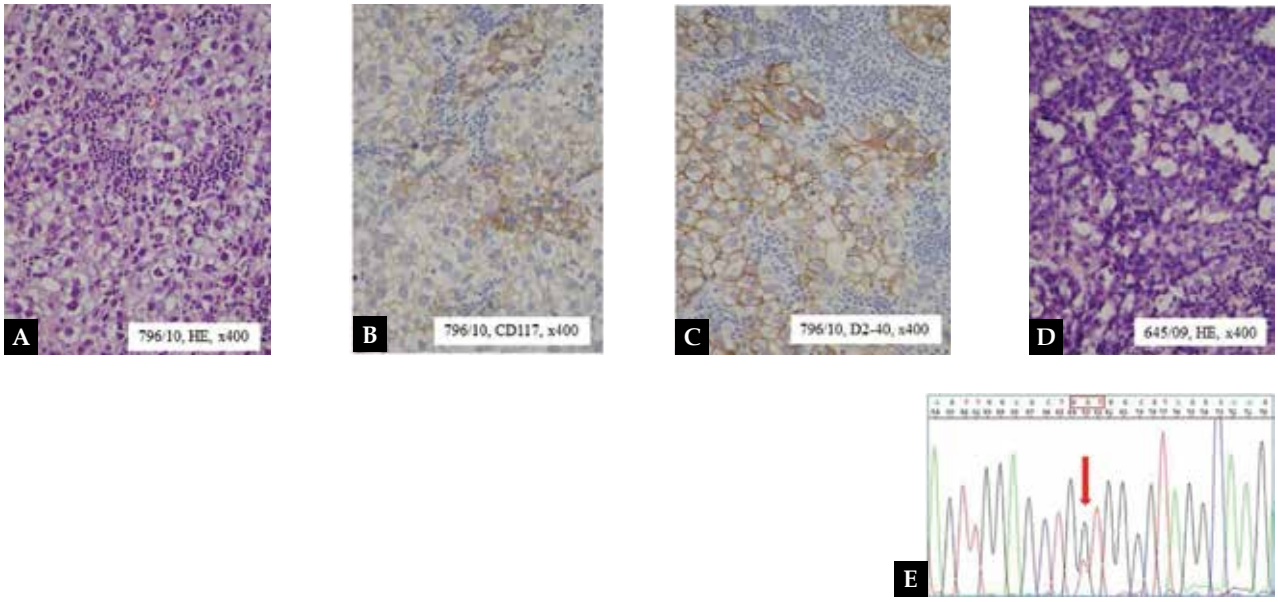

Figure 2A. *Haematoxylin and eosin (HE) stain of tumour tissue of Patient 1. Tumour tissue is composed of nests of large polygonal cells with distinct cell borders, interspersed with lymphocytes. Tumour cells had ample, clear cytoplasm and centrally positioned, round, vesicular nuclei with prominent nucleoli;* **B, C.** *Immunohistochemical stain of tumour tissue of Patient 1 demonstrated tumour cells positive on CD117 and D2-40, OCT-4 and CK (AE1/AE3), and negative on CD30 and αFP;* **D.** *Haematoxylin and eosin (HE) stain of tumour tissue of Patient 2. Tumour tissue shows lobules of large cells with abundant, clear cytoplasm and round, vesicular nuclei, intermingled with numerous lymphocytes;* **E.** *Confirmation of detected variant in KRAS gene in Patient 1 by direct sequencing-missense variant noted as rs121913529 (c.35 G>T, p.G12V). Codon GGT coding for amino acid glycine is transformed into codon GTT for amino acid valine*

Rycina 2A. *Barwiony hematoksyliną-eozyną (HE) preparat tkanki guza Pacjenta 1. Guz składa się z gniazd dużych komórek poligonalnych w wyraźnymi granicami komórek otoczonych przez limfocyty. Komórki nowotworowe zawierają dużo przejrzystej cytoplazmy oraz centralnie umiejscowione okrągłe, pęcherzykowate jądro z wyraźnym jąderkiem;* **B, C.** *Barwienie immunohistochemiczne tkanki guza Pacjenta 1. Widoczne komórki nowotworowe z dodatnią reakcją z CD117 i D2-40, OCT-4 and CK (AE1/AE3), a ujemną z CD30 i αFP;* **D.** *Barwiony hematoksyliną-eozyną (HE) preparat tkanki guza Pacjenta 2. Guz jest zbudowany ze zrazików złożonych z dużych komórek z dużą ilością przejrzystej cytoplazmy z okrągłym, pęcherzykowatym jądrem, pomiędzy którymi znajdują się liczne limfocyty;* **E.** *Potwierdzenie wykrytego wariantu w genie KRAS u Pacjenta 1 przez bezpośredni odczyt sekwencji "missense" rs121913529 (c.35 G>T, p.G12V). Kodon GGT kodujący glicynę został zamieniony na kodon GTT kodujący walinę*

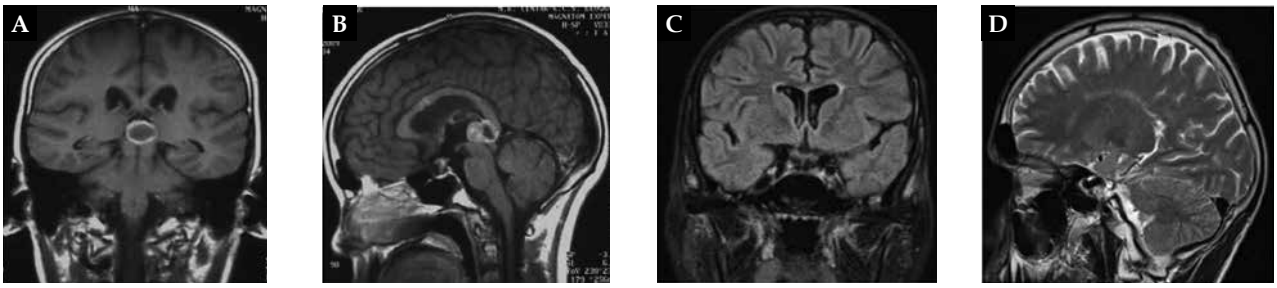

Figure 3A, B. *Preoperative MRI of Patient 2 showed tumour in the third ventricle and pineal region, with hydrocephalus and dilatation of both lateral ventricles;* **C, D.** *MRI of Patient 2, seven years after radiotherapy and chemotherapy and two years of GH replacement, shows no signs of tumour recurrence*

Rycina 3A, B. *Przedzabiegowe badanie MRI Pacjenta 2 z widocznym guzem w okolicy trzeciej komory i szyszynki oraz wodogłowiem i poszerzeniem obu komór bocznych;* **C, D.** *Badanie MRI Pacjenta 2 wykonane siedem lat po radioterapii i chemoterapii oraz dwa lata po rozpoczęciu terapii zastępczej GH. Nie ma żadnych cech nawrotu nowotworu*

height, and at the age of 18 years he was admitted to neuroendocrine department where hormonal evaluation confirmed diabetes insipidus and isolated GHD. He had normal BMD, and QoL had decreased. Cranial and spinal MRI excluded tumour recurrence. Five years after the complete remission, growth hormone substitution was recommenced. The starting dose of GH was 0.4 mg daily, which was the dose of maintenance. Close follow-up every six months for two years showed IGF1 normalisation, improvement of body composition (Table II), and better QoL with no signs of tumour presence on MRI (Figures 3C, D).

Genetic analysis — method and result

Genomic DNA was extracted from formalin-fixed, paraffin-embedded samples of tumour tissues (FFPE) using a QIAmp DNA Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. The patient was genetically diagnosed by next-generation sequencing (NGS) using the Illumina Clinical-Exome Sequencing TruSight One Gene Panel. Annotation and filtering of variants were performed using VariantStudio 3.0 Data Analysis Software (Illumina, San Diego, CA). After detection of the pathogenic variant in the analysed patient, we designed specific primers for Sanger sequencing in order to confirm the result, using the NGS approach. PCR fragments were directly sequenced using a Big Dye terminator cycle sequencing kit and an ABI PRISM 310 automated sequencer (Applied Biosystems Life Technologies, USA). Missense mutation was analysed with PolyPhen-2, SIFT, and MutPred software, to predict whether an amino acid substitution affects protein function.

In order to determine the genetic basis of Patient 1 we used TruSight One Gene Panel and generate VCF file. We prioritised 21 genes present in the panel (AASS, BCORL1, BRAF, CBL, FGFR2, GIMAP8, HRAS, JMYD1C, KIT, KRAS, NF1, NRAS, MAPK8, MAPK10, PI3K, PTEN, PIK3R2, PTPRB, PDGFRA, RASA1, and TRAF6), and detected the variant within exon 2 in the KRAS gene (NM_033360.3, c.35G>A, p.G12V). This genetic variant is predicted to be pathogenic according to ClinVar and dbSNP, and deleterious and possibly damaging according to Sift and PolyPhen, respectively. The result gained using the NGS approach was confirmed by Sanger sequencing.

Discussion

Intracranial germ cell tumours (ICGCT) account for about 3% of all brain tumours in children younger than 15 years, usually occuring between 10 and 14 years of age. Their incidence is significantly higher in Japan, at 15.4%, than in Western Europe, at 3.6% [1]. ICGCT generally develops in the midline, most frequently in the pineal region and the suprasellar area, and these tumours can also occur in the basal ganglia and/or thalamus [2]. According to WHO classification there are two main histological types of these tumours: pure germinoma and non-germinoma, which includes embryonal carcinoma, teratoma, yolk sac tumour, and choriocarcinoma [3]. The most common are pure germinoma, while about 30% of ICGCT are mixed forms of these five histological types.

We presented two brothers with a history of intracranial pure germinoma. To our knowledge, only six reports describing the phenomenon of familial ICGCT have been published so far, three of which related to pure germinoma [4–9]. Until recently it was thought that these familial tumours occurred only in siblings, but a later report described intracranial germinoma (ICG) in father and son [9]. All of the described cases are Japanese. Whether race or environmental factors are associated with the obviously high incidence of familial ICG in Japan is unknown. Our patients are Caucasians

of Serbian ethnicity. The presence of ICG in one member and the development of other suprasellar lesions in first-degree relatives has been reported. It included three family members: a mother with a Rathke's cleft cyst, one daughter who suffered from intracranial germinoma, and the other daughter who had a pituitary cyst [10]. Recently, a report of pineal region mixed mature teratoma and germinoma in two fraternal brothers of fraternal triplets has been published [11].

The cell of origin of intracranial GCTs is still controversial, and the molecular mechanism of tumorigenesis remains unclear. Because of the scarcity of tissue samples available, very little basic research had been carried out, and the biology of ICG is poorly understood. Since the familial ICGCT is mainly observed in siblings within the family, it was considered that their inheritance might be autosomal recessive [8]. However, a recent study has described ICGCT in the father and son, which suggests a more complex pattern of inheritance [9]. Several candidate genes have been investigated, which could be included in the aetiology of these tumours — KIT, KRAS, NANOG, NRAS, CCND, BRAF [12]. The strongest evidence is that KIT gene mutation results in activation of specific ligand stem cell factor (SCF), which has a prominent role in cell proliferation in ICGCT via mitogen-activated protein kinase (MAPK) pathway [13]. Fukushima et al. examined the KIT signalling pathway in 65 patients with sporadic ICGCT, of which 30% are pure germinoma [14]. While the mutation in KIT gene was by far the most frequently presented (40.0%), the alterations in RAS genes (KRAS, NRAS, HRAS, RRAS2) were collectively the second most common events in pure germinoma (20.0%). Similarly, a large study by Ishimura et al. demonstrated that mutually exclusive mutations of genes involved in the MAPK pathway were most common (48.4%), typically in KIT (27.4%) and RAS genes (12.2%), followed by those in the PI3K pathway (12.9 %), particularly in MTOR (6.5%), among the 124 patients with ICGCT [15]. We performed genetic analysis in tumour tissue of Patient 1 and confirmed a somatic alteration in exon 2 of the KRAS gene, noted as rs121913529 (c.35 G>T, p.G12V). For this KRAS missense pathogenic variant is known to be a common genetic aberration involved in cancerogenesis, which was previously reported in colorectal and lung cancer and leukaemia [16–18]. A study by Wang et al. reported a significant enrichment of novel and rare germline variants in JMJD1C, a histone demethylase and coactivator of the androgen receptor, among Japanese IGCT patients as compared to a non-Japanese cohort [19]. Several cases of ICG associated with chromosomal abnormalities have been reported, which include patients with Down's syndrome and Klinefelter syndrome [20, 21]. A recently published study showed that pure germinomas are characterised by global low DNA methylation, a unique epigenetic feature making them distinct from all other ICGCT subtypes. The MAPK and/or PI3K pathway alterations, global low DNA methylation, and chromosomal instability form a triad that contributes in the pathogenesis of ICGCT [22]. Due to the rarity of familial occurrence of ICG, there is no data in the literature of their pathogenesis.

Since ICG affect the region of the pituitary gland and the hypothalamus, clinical manifestations of these tumours include diabetes insipidus, which is usually the first symptom, followed by visual abnormalities, hydrocephalus, and hypopituitarism [23]. Hypopituitarism in patients with ICG is usually the consequence of radiotherapy [24]. In addition to radiotherapy, the tumour size, the invasion of surrounding structures, and the extent of surgery are crucial for pituitary function in these patients. GH deficiency is present in 89–95% of ICGCT, in a similar percentage as in hypogonadism, while hypothyroidism and hypocorticism are present in about 50% of patients [25–27]. Our patients had IGHD, and the younger brother had suffered from diabetes insipidus, which persisted after remission. Interestingly, despite the extensive surgery in the older brother and high doses of radiotherapy in both patients, only IGHD was confirmed in both. Five-year survival after the radiotherapy of pure germinoma was over 90%. Cases of relapse of ICG after 14 and 17 years from radiotherapy have been reported [28–30]. So far, the longest described relapse was 23 years from treatment in a female patient treated with multiple hormone replacement therapy including GH [31].

Growth hormone may enhance cell proliferation and tumorigenesis, and therefore, as a replacement therapy, it may potentially increase the risk of secondary neoplasms (SN) or recurrence of the primary tumour. According to the evidence from the long-term follow-up of thousands of patients, the GH safety profile remains satisfactory [32, 33]. However, a few studies in childhood cancer survivors have shown that GH may induce a modest increase in the relative risk of occurrence of SN, especially in those treated with radiotherapy, and that risk declines over time [34, 35]. On the other hand, adults with GHD and a history of childhood cancer have not demonstrated an increased cancer risk during GH replacement. Our two patients with history of malignancy in childhood were successfully treated with growth hormone as young adults, four and five years after complete remission. The two years of GH replacement therapy improved body composition and QoL. On the other hand, their BMD did not change (Patient 1), but even decreased (Patient 2). The possible reason for this outcome is the short period of GH replacement for the full expression of its anabolic effect on the bone. Since the pathogenesis and genetic backgrounds of

familial ICG are unclear, we speculated that familial ICG may be more susceptible to relapse than sporadic cases. Because of this assumption, we were especially careful in making a decision on the introduction of GH therapy in the presented patients.

To our knowledge, this is the first case that describes familial intracranial germinoma outside Japan and the seventh case reported so far.

Declaration of interest

The authors declare that they have no conflict of interest.

Authorship

Treatment of intracranial germinoma is multidisciplinary, so the author list consists various medical specialties. Regarding the author list, I, as the first author (M. Doknic, MD, PhD, ass. prof, endocrinologist) am the creator of the work, the interpreter, and the writer of the manuscript. Neurosurgeons Savic D. MD, PhD, ass. prof and Grujicic D., MD, PhD, prof. performed surgery in both patients, while radiologist Bokun J., MD, PhD was responsible for radiotherapy in both patients. Histopathological and immunohistochemical diagnoses were established by two pathologists Manojlovic-Gacic E., MD, PhD ass. prof and Raicevic S., MD, PhD. The two presented patients were followed by their paediatrician Milenkovic T., MD, PhD during paediatric age. The first author with other endocrinologists in the author list (Pekić S., MD, PhD, ass. prof; Miljić D., MD, PhD, ass. prof; Stojanović M., MD, ass. prof. and Petakov M., MD, PhD, prof.) followed and treated the presented patients regarding pituitary function and growth hormone replacement.

Hence, all co-authors made a significant scientific contribution to this article.

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