CASE REPORT

Neurogenic fever in a patient with a chordoid glioma

Rafael García Carretero,¹ Marta Romero Brugera,² Oscar Vazquez-Gomez,³ Noelia Rebollo-Aparicio²

¹Hospital Universitario de Mostoles, Mostoles, Spain

²Department of Emergency, Hospital Universitario de Mostoles, Mostoles, Spain

³Department of Infectious Diseases, Hospital Universitario de Mostoles, Mostoles, Spain

Correspondence to
Dr Rafael García Carretero,
rgcarretero@salud.madrid.org

Accepted 4 November 2016

SUMMARY

Chordoid gliomas are rare tumours. Despite being considered low-grade neoplasms, recent reviews have reported generally poor prognosis due to complications involving severe hypothalamic symptoms. We report a patient aged 30 years with chordoid glioma. What makes this case report interesting is the presence of neurogenic fever, which was already present before the final diagnosis of the brain tumour and also several months after the surgical removal. Since the patient underwent a subtotal resection of the tumour, it remains unclear whether the fever was due to hypothalamic dysfunction or remnants of the tumour. We also performed temperature logging with a continuous-monitoring recording device.

BACKGROUND

Chordoid glioma is considered a rare brain neoplasm, first described two decades ago. There are few case reports published on chordoid gliomas, and although the clinical data collected do not allow us to reach definitive conclusions that would shed light on the natural history of the disease, some case series have highlighted some issues regarding clinical presentation, optimal treatment, postoperative complications and prognostic factors.

Regarding neurogenic (or centrally mediated) fever, it is believed that a hypothalamic injury is involved, leading to its failure as a thermoregulatory centre.

CASE PRESENTATION

A male patient aged 30 years was admitted to the hospital with hypaesthesia and paraesthesia on the right side of the face, mild dysarthria and mild headache.

On examination, he had dysarthria, paralysis of the right facial nerve, right eyelid drooping and decreased sensation and numbness in the right side of the face (hypaesthesia).

The patient underwent a perimetry test (visual field test), which revealed homonymous inferior quadrantanopia. The rest of the neurological examination was unremarkable. According to the neurologist, the dysarthria was due to the paralysis of the facial nerve and the difficulty in pronunciation of words, as opposed to a problem with the production of language. The neurologist therefore diagnosed him with Bell's palsy, and steroid treatment was initiated with prednisone 60 mg daily. However, the field of vision was affected and a

lesion of the optic chiasm was suspected, so the patient underwent a CT and MRI scan.

INVESTIGATIONS

Initial laboratory tests showed a normal complete blood count; liver and kidney function were also normal, as was the chest X-ray. The MRI showed a mass with lobulated borders in the suprasellar region and extension into the third ventricle and the hypothalamus, isointense on T1-weighted imaging, slightly hyperintense on T2-weighted imaging and enhancing on contrast administration (figure 1). The mass was 3×2.7×2.2 cm and did not affect the pituitary. The lateral ventricles were normal in size, and the mass was not causing hydrocephalus.

DIFFERENTIAL DIAGNOSIS

There are some masses that arise in the suprasellar region, hypothalamus or the third ventricle, such as pituitary adenoma, chordoid meningioma, ependymoma, craniopharyngioma or metastases from another primary tumour. Given the localisation and the radiological features of the tumour, the first diagnostic hypothesis was a chordoid glioma. Chordoma and chordoid meningioma (both chordoid neoplasms) are the main differential diagnoses, that should be ruled out with immunohistochemistry techniques.

TREATMENT, OUTCOME AND FOLLOW-UP

The patient was referred to our Neurosurgery Department and he underwent a bifrontal craniotomy procedure with an interhemispheric trans-callosal approach; a subtotal resection was performed. At intraoperative examination, medium-consistency, multilobulated, encapsulated mass was firmly attached

Figure 1 Two slides showing a lobulated mass in the suprasellar region, which enhances after endovenous contrast, in a T1-weighted imaging sagittal plane (slide A) and in a T2-weighted imaging coronal plane (slide B).

CrossMark

To cite: García Carretero R, Romero Brugera M, Vazquez-Gomez O, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-218205

to the optic chiasm and the hypothalamus. These findings played a role in determining the extension of the resection.

Two months later, he received adjuvant focal fractionated radiotherapy in several sessions (48.6 Gy in total), but due to the poor tolerance of this treatment, the patient also underwent Gamma Knife radiosurgery, delivering a lower marginal dose of 11.0 Gy following the subtotal resection, in order to minimise morbidity and improve the tolerance. The patient did not receive chemotherapy.

Pathological examination showed an epithelioid tumour arranged in cords and clusters. Immunohistochemistry demonstrated its cells were positive for TTF-1 and GFAP. These findings were consistent with the diagnosis of chordoid glioma.

In the months that followed, the patient developed several postsurgical complications. Immediately after the surgical intervention, he presented with transient central diabetes insipidus, which disappeared before he was discharged. The patient presented with weaknesses, writing disabilities, fluctuating spatial disorientation, learning disabilities, dyslexia, attention deficits, behavioural changes, compulsive behaviour, obesity due to abnormal eating habits, irritability, memory disturbances and aggressive behaviour.

The patient also presented with panhypopituitarism, for which he was taking hydrocortisone 10 mg twice a day and L-thyroxine 150 µg daily. He was also taking topiramate 100 mg twice a day and risperidone 1.5 mg at night.

After 1 year of follow-up, the cognitive and behavioural abnormalities had not improved. His wife, however, drew our attention to another problem: his history of fever. He had been presenting with intermittent fever since 1 month after he was discharged for the first time and had not stopped since then. He did not present with malaise, chills, dizziness or fatigue. When his wife noticed a high temperature (up to 38.8°C), she took his temperature in the armpit using a digital thermometer. His temperature could vary from normal to fever levels during the same day, and sometimes fever occurred 1 day and recurred between 1 and 3 days later, with no obvious pattern. This fever was not accompanied by chills or malaise, as mentioned, and it did not disappear with painkillers such as ibuprofen, naproxen or indomethacin. His general practitioner recommended treatment with levofloxacin 500 mg daily for 10 days, but there was no significant improvement.

Overall, the patient's temperature had rarely been above 38°C since he was discharged, but in the 2 weeks before, he was admitted to the hospital for the second time, he had a temperature above 38.8°C every 2 or 3 days.

We decided to perform a complete workup to rule out infectious or inflammatory causes, and the patient was therefore admitted for the second time 18 months after the diagnosis of the tumour. Blood and urine cultures were negative. Kidney and liver functions were normal. There was no leucocytosis or neutrophilia. Acute-phase reactants such as C reactive protein and procalcitonin were normal.

C3 and C4 levels, antineutrophil cytoplasmic antibody and antinuclear antibody tests were also normal. A chest X-ray and abdominal CT scan were performed, which did not show any abnormalities. In order to rule out infective endocarditis, a trans-thoracic echocardiography was performed, which was normal. Deep vein thrombosis was ruled out by performing an ultrasonography of the lower limbs. We also decided to perform a brain MRI, which showed remnants of the tumour in the anterior wall of the third ventricle, which was compressing the optic chiasm (figure 2). However, it did not show any changes compared with the postoperative brain MRI.

Figure 2 T1-weighted imaging axial plane slides. Slide A showing the neoplasm prior to the surgical procedure; slide B showing the tumour after surgical and radiotherapy treatment, 1 year later.

We eventually decided to search for a pattern in the fever, so we used a TherCom device for temperature monitoring with a tympanic probe (a thermistor sensor was placed in the external auditory canal).^{1 2} The line chart is shown in figure 3.

The patient was discharged 15 days later, having been diagnosed with neurogenic fever. We had ruled out infectious and inflammatory conditions, as well as deep vein thrombosis.

One month later (20 months after surgical resection), he was admitted to the hospital for a third time, presenting with dyspnoea, malaise and syncope. His blood pressure was 90/50 mm Hg, heart rate was 110 bpm and arterial oxygen saturation was 90%. A CT scan showed an acute massive pulmonary thromboembolism, so he was placed in the intensive care unit (ICU). Fibrinolytic therapy was considered too risky because of the intracranial surgery. The patient died in the ICU 36 hours after his admission.

DISCUSSION

Chordoid glioma is a rare brain tumour, first described in 1998 by Brat *et al.*³ According to the WHO, this tumour is a low-grade neoplasm. Chordoid glioma usually arises in the anterior portion of the third ventricle. There have been two major case series: in 2007, a Spanish group reviewed 40 cases,⁴ and later, in 2015, Ampie *et al.*⁵ performed a systematic review of 81 patients. Bielle *et al.*⁶ reported a case study which included the histopathological and immunohistochemical features of 17 patients who had been diagnosed with chordoid glioma, and concluded that TTF-1 can be a useful marker for the differential diagnosis of this rare tumour.

The clinical presentation and most of the complications arise due to it being located near the hypothalamus, affecting critical structures within the brain.⁵ Given this characteristic location, almost all patients presented with symptoms such as visual deficits, behavioural changes, speech difficulties, symptoms related to obstructive hydrocephalus, hypothalamic dysfunction and endocrine dysfunction. In the case series by Ampie *et al.*,⁵ the tumour was incidental in three patients, since they did not present symptoms. In our patient, we believe the diagnosis of the neoplasm was incidental. Our neurologist diagnosed him with Bell's palsy, but we considered it to be unrelated to the tumour.

On physical examination, however, the only neurological symptom was a visual deficit, which went unnoticed by the patient.

Figure 3 Line chart showing the 24-hour period in which the temperature of the patient was monitored. The blue, dashed line represents 37.6°C. Temperature measurements were taken every minute over a 72-hour. We represent here a 24-hour period.

This neoplasm is usually a non-invasive, well-circumscribed, oval-shaped tumour, located within the third ventricle, near critical structures such as the pituitary and the hypothalamus.⁴ Neuroimaging of chordoid glioma is not consistent regarding signal intensity on CT scan. On MRI, however, the tumour can be isointense or hypodense, and it enhances on contrast administration in T1-weighted imaging.⁵

With regard to surgical treatment, three approaches have been described: trans-cortical, trans-callosal and trans-lamina terminalis. The surgical approach does not seem to be a prognostic factor, as it is the extent of tumour resection.⁵ Gross total resection is associated with improved outcomes, whereas progression of the tumour was present in a high rate after biopsy alone or subtotal resection. It should be mentioned, however, that most of the deaths were not related to the recurrence of the tumour or progression of the disease, but rather to postoperative complications.

Nonetheless, surgical approach does appear to be a prognostic factor regarding complications and morbidity. The tumour can be adhered to the hypothalamus, and an extensive resection can lead to hypothalamic dysfunction, memory deficits, visual injury, seizures and behavioural changes.

Radiotherapy can be used as an adjuvant therapy, although its role remains unclear. Gamma Knife radiosurgery and focal fractionated radiotherapy have been used, delivering 10.5–12 and 54 Gy, respectively, especially associated with biopsy alone or subtotal resection, in order to minimise postoperative complications.⁷

The 5-year overall survival is 63.7%,⁵ but as previously mentioned, the deaths could not be attributed to progression of the tumour, but rather to myocardial infarction, infections and pulmonary embolism. The latter has been reported in five cases, and our patient would be the sixth case.

With regard to neurogenic fever, it is known that raised temperature after brain damage may be caused by an injury to the hypothalamus, even though inflammatory and infectious conditions must be ruled out.⁸ This means that we should distinguish between fever (regulated adjustment in response to inflammation or infection) and neurogenic hyperthermia (unregulated temperature rise due to brain damage), but these diagnoses are difficult to make clinically.^{8,9}

A functional thermostat or central set-point in mammals regulates the temperature. This neural network for thermoregulation lies within the preoptic and the anterior hypothalamus areas in the brain.^{8,10}

For clinicians, fever can be recognised as a condition in which patients are presenting with sweating, cold and shivers. The hypotheses are that the body is hypothermic relative to the set-point, which has been readjusted as a response to infectious or inflammatory diseases. This would therefore be a physiological response.⁸

However, after a severe or traumatic brain injury, damage to the hypothalamus or its pathways may pathologically readjust the set-point, and central fever (also known as neurogenic hyperthermia) can occur. Diffuse axonal or frontal lobe injuries are likely to be the underlying conditions in developing neurogenic fever.⁹

This failure in thermoregulatory control can be difficult to diagnose, and that is why other conditions must be ruled out first. Clinicians should make a diagnostic workup to assess sepsis, drug side effects, deep venous thromboembolism and inflammatory diseases.

Patient's perspective

- We contacted the patient's wife in order to obtain consent and we asked for her comments or suggestions regarding this manuscript. Here is what she wrote:
- I agree with the content and the description of the clinical presentation, but I would like to highlight some additional aspects. Although the behavioural changes were quite accurate in your descriptions, some other subtle features should be mentioned, as I acknowledged that my husband was not the same person I had married some years ago. He had lost his motivation and sense of humour and had become dull. While I was affected by his death, I felt that I had lost my husband soon after the surgical resection. He was not able to return to work or keep up with friends and family.

Learning points

- ▶ Chordoid gliomas are rare tumours, but despite their low histological grade, their adherence to critical structures within the brain means that they are associated with poor prognosis. Severe postsurgical morbidity and hypothalamic symptoms are frequent.
- ▶ Gross total resection yields lower recurrence rates and is considered the treatment of choice, but it is associated with an increased risk of postsurgical morbidity. Clinicians should be aware of these complications, such as deep vein thrombosis, in order to minimise them.
- ▶ Neurogenic fever, or central hyperthermia, is a non-infectious condition that may arise in patients with severe hypothalamic injury. As a diagnosis of exclusion, an exhaustive workup should be performed to rule out life-threatening conditions, such as sepsis or thrombotic events.

Neurogenic hyperthermia is therefore a diagnosis of exclusion,⁹ and in our patient, we ruled out infectious diseases by performing urine and blood cultures, serum biomarkers (procalcitonin and C reactive protein), autoimmunity tests and an abdominal CT scan. Our patient did not present tachycardia, chills or diaphoresis at any time, and the fever was resistant to antipyretic medication. This is why we believe the origin of this non-infectious fever was central hyperthermia or neurogenic fever.

We decided to monitor the temperature using a TherCom device to record a log every minute over a 72-hour period (figure 2). The resulting graph was rendered using R programming language, V3.1.1 (R Core Team. R: A Language and Environment for Statistical Computing [internet]. Vienna, Austria; 2014. Available from: <http://www.r-project.org/>) and its package ggplot2.¹¹

Finally, the patient's clinical outcome was poor, as he passed away due to a thrombotic complication, and not due to

progression of his disease (chordoid glioma). Along with the previously reported cases of thrombosis associated with chordoid glioma,^{4 5 12} our patient would be the sixth reported case.

Twitter Follow Rafael García Carretero at @rafa_linux

Contributors RGC wrote the first draft; MRB and OV-G made interesting suggestions; NR-A helped in the translation into English.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cuesta-Frau D, Varela M, Aboy M, *et al*. Description of a portable wireless device for high-frequency body temperature acquisition and analysis. *Sensors (Basel)* 2009;9:7648–63.
- 2 Varela M, Cuesta D, Madrid JA, *et al*. Holter monitoring of central and peripheral temperature: possible uses and feasibility study in outpatient settings. *J Clin Monit Comput* 2009;23:209–16.
- 3 Brat DJ, Scheithauer BW, Staugaitis SM, *et al*. Third ventricular chordoid glioma: a distinct clinicopathologic entity. *J Neuropathol Exp Neurol* 1998;57:283–90.
- 4 Ortega-Martinez M, Cabezu JM, Bernal-Garcia LM, *et al*. [Chordoid glioma of the III ventricle. Case report and revision of the literature]. *Neurocirugia (Astur)* 2007;18:115–22.
- 5 Ampie L, Choy W, Lamano JB, *et al*. Prognostic factors for recurrence and complications in the surgical management of primary chordoid gliomas: a systematic review of literature. *Clin Neurol Neurosurg* 2015;138:129–36.
- 6 Bielle F, Villa C, Giry M, *et al*. Chordoid gliomas of the third ventricle share TTF-1 expression with organum vasculosum of the lamina terminalis. *Am J Surg Pathol* 2015;39:948–56.
- 7 Kobayashi T, Tsugawa T, Hashizume C, *et al*. Therapeutic approach to chordoid glioma of the third ventricle. *Neurol Med Chir (Tokyo)* 2013;53:249–55.
- 8 Childs C. Human brain temperature: regulation, measurement and relationship with cerebral trauma: part 1. *Br J Neurosurg* 2008;22:486–96.
- 9 Thompson HJ, Pinto-Martin J, Bullock MR. Neurogenic fever after traumatic brain injury: an epidemiological study. *J Neurol Neurosurg Psychiatr* 2003;74:614–19.
- 10 Meier K, Lee K. Neurogenic fever: review of pathophysiology, evaluation, and management. *J Intensive Care Med* 2016.
- 11 Wickham H. *ggplot2: elegant graphics for data analysis* [internet]. New York: Springer, 2009. <http://had.co.nz/ggplot2/book>.
- 12 Bongetta D, Risso A, Morbini P, *et al*. Chordoid glioma: a rare radiologically, histologically, and clinically mystifying lesion. *World J Surg Oncol* 2015;13:188.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow