Familial chordoma
A REPORT OF TWO CASES

A. K. Bhadra, A. T. H. Casey
From National Hospital for Neurology & Neurosurgery, London, England

We have treated 175 patients with a chordoma over a ten-year period. Only two had a family history of the condition and we describe these in this paper. In one patient the tumour was at the craniocervical junction and in the other the lesion affected the sacrum. We have undertaken a literature review of familial chordoma and have identified chromosomal abnormalities associated with the condition.

Chordomas are rare tumours which arise from embryonic notochordal remnants along the length of the neuraxis at developmentally-active sites, such as the ends of the neuraxis and the vertebral bodies. Although chordomas comprise only 0.2% of all tumours of the central nervous system, they do constitute 2% to 4% of all primary bone tumours. In addition, they can occur in extra-axial locations. Approximately 35% of chordomas arise at the base of the skull, 50% in the sacrococcygeal region, and the remaining 15% in the vertebral bodies.1

We describe two patients who underwent surgery for a chordoma, one at the craniocervical junction and the other in the sacrum. Both had a family history of a chordoma.

Case 1
A 46-year-old Caucasian woman presented with diplopia, which developed during her second pregnancy. There had been an episode of diplopia approximately three years previously which had resolved spontaneously without treatment. She had no headache, vomiting or limb weakness. A dermoid cyst had been removed from the sacral region at the age of 21 years.

On clinical examination the only positive finding was a right VIth cranial nerve palsy. An MRI scan of the brain and upper cervical spine showed a bony lesion in the upper part of the clivus (Fig. 1). She underwent an excision of the clival chordoma through a transoral and transpalatine approach, followed by post-

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Fig. 1
Case 1 – Clival chordoma. Sagittal MRI scan (T1-weighted image) showing a bony lesion at the upper part of the clivus (arrow).
operative stereotactic radiotherapy. Annual follow-up showed no recurrence eight years later.

**Family history.** She had a strong family history of chordoma. First, her sister presented with a clival chordoma at the age of seven years, underwent five operations because of recurrence and eventually died at the age of 25 years. Secondly, her cousin (maternal uncle’s daughter) had a clival chordoma at the age of 22 years, was deaf and had undergone repeated operations. Six other members of her family had a positive histological diagnosis for chordoma (mostly clival) (Fig. 2).

**Histology.** The tumour comprised small groups of cells within an Alcian-blue-positive matrix. The cells had a variable amount of PAS-positive cytoplasm, mild nuclear pleomorphism and no mitotic figures. Immunohistochemical staining for S-100 protein and cytokeratin was positive. The appearances were all those of a chordoma (Fig. 3).

**Genetic study.** Genetic analysis of the patient and her relatives (National Cancer Institute, Bethesda, Maryland) showed a loss of heterozygosity on the 7q chromosome.

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**Case 2**

A 25-year-old South African white woman presented with an eight-month history of lumbar back pain, recurrent urinary tract infections and incomplete bladder emptying. She had a past history of a clival chordoma, which had been resected at the age of three years. At the age of six years she developed a sacral mass (chordoma at S2-S4), with apparent bony involvement. This was incompletely resected and she received radio- and chemotherapy. At the age of 19 years she presented with a three-month history of back pain and underwent a further attempt to remove her tumour. Post-operatively, she developed urinary incontinence and a bilateral drop foot. On clinical examination she had an absent right ankle reflex, reduced power of dorsiflexion and
plantar flexion, and a sensory deficit over the L5 and S2-S4 dermatomes. An MRI scan of the lumbar and sacral regions showed a recurrence, with extensive sacral replacement by chordoma, both anteriorly and posteriorly (Fig. 4). She underwent a further palliative debulking procedure through a posterior approach, followed by post-operative radiotherapy. She was reviewed annually but died three years later. The exact cause of death is not known.

**Family history.** There were two other family members who had been affected by a chordoma. Her paternal grandmother had a clival chordoma at the age of 32 years, from which she died and her father had died of a clival chordoma at the age of 55 years.

During the course of our investigation we unexpectedly found that our two patients were distantly related and that the great great grandparents of our first case had originally lived in South Africa.

**Histology.** The tumour was composed of cords, with nests and sheets of cells containing an abundant, vacuolar cytoplasm. There were areas of fibrosis, necrosis and inflammation. Immunohistochemistry showed positive staining for S-100 protein and cytokeratin (Fig. 5).

**Genetic study.** We were unable to carry out a genetic study as she did not have any living relatives.

**Discussion**

Chordomas are adult epithelial tumours arising from embryonic notochord remnants of the axial skeleton. They are slow-growing, locally-invasive bone tumours.1–3 The age-adjusted incidence of chordomas is 0.08 per 100 000. It is more common in men than women,4 the mainstay of treatment being excision followed by radiotherapy.5 Our study documents two patients with familial chordoma and their surgical management. Only a few families with chordoma have been reported since 1958 (Table 1).6

There are few familial cases of chordoma. In our hospital, which accepts tertiary referrals, we have only treated two such patients out of a total of 175 over a ten-year period (1995 to 2005). In this complete series the craniocervical junction was involved in 79 patients (45.1%), the sacral area in 92 (52.6%) and the thoracic and lumbar spine in four (2.3%).

A genome-wide analysis for linkage in a family with ten members affected by chordoma showed the chromosomal locus for familial chordoma to be 7q33. Our first patient was part of this study.3

A further study involving a father, recurrent clival chordoma and his two daughters, affected by a cerebral astrocytoma and clivus chordoma, respectively, identified the region from 1p36.31 to 1p36.13 as a probable locus involved in susceptibility to familial and sporadic chordoma formation.2,7

A more recent study8 analysed a series of 22 skull-base chordomas and showed isochromosome 1q to be the sole recurring structural chromosome rearrangement.8 We hope that further genetic studies might give insight into the pathogenesis and treatment of this rare type of tumour.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**References**


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**Table I. Reported cases of familial chordoma found from our literature search, using ‘familial chordoma’ as the key term**

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Number of patients</th>
<th>Site</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelley et al²</td>
<td>10</td>
<td>Clivus/nasopharynx – 9, sacral – 1</td>
<td>Linked to chromosome 7q33</td>
</tr>
<tr>
<td>Miozzo et al⁷</td>
<td>3</td>
<td>Father-clivus</td>
<td>Tumour suppressor locus maps to 1p36</td>
</tr>
<tr>
<td>Dalpra et al²</td>
<td>4</td>
<td>2nd Daughter – cerebral astrocytoma</td>
<td>Probable autosomal dominant inheritance</td>
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<tr>
<td>Stepanek et al⁹</td>
<td>3</td>
<td>A male-sacral chordoma</td>
<td></td>
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<tr>
<td>Kerr et al⁶</td>
<td>3</td>
<td>First cousin – nasopharyngeal</td>
<td></td>
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<tr>
<td>Enin¹⁰</td>
<td>2</td>
<td>A male – nasopharyngeal chordoma</td>
<td></td>
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<tr>
<td>Foote, Ablin and Hall¹¹</td>
<td>2</td>
<td>Brother – sacral</td>
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**Key Points**

- Chordomas are slow-growing, locally-invasive bone tumours.
- They are more common in men than women.
- The age-adjusted incidence of chordomas is 0.08 per 100 000.
- There are few familial cases of chordoma.
- A genome-wide analysis for linkage in a family with ten members affected by chordoma showed the chromosomal locus for familial chordoma to be 7q33.
- A further study involving a father, recurrent clival chordoma and his two daughters, affected by a cerebral astrocytoma and clivus chordoma, respectively, identified the region from 1p36.31 to 1p36.13 as a probable locus involved in susceptibility to familial and sporadic chordoma formation.
- A more recent study analysed a series of 22 skull-base chordomas and showed isochromosome 1q to be the sole recurring structural chromosome rearrangement.