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Spinal cord tumours: advances in genetics and their implications for treatment

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Abstract

Tumours of the spinal cord, although rare, are associated with high morbidity. Surgical resection remains the primary treatment for patients with this disease, and offers the best chance for cure. Such surgical procedures, however, carry substantial risks such as worsening of neurological deficit, paralysis and death. New therapeutic avenues for spinal cord tumours are needed, but genetic studies of the molecular mechanisms governing tumourigenesis in the spinal cord are limited by the scarcity of high-quality human tumour samples. Many spinal cord tumours have intracranial counterparts that have been extensively studied, but emerging data show that the tumours are genetically and biologically distinct. The differences between brain and spine tumours make extrapolation of data from one to the other difficult. In this Review, we describe the demographics, genetics and current treatment approaches for the most commonly encountered spinal cord tumours—namely, ependymomas, astrocytomas, haemangioblastomas and meningiomas. We highlight advances in understanding of the biological basis of these lesions, and explain how the latest progress in genetics and beyond are being translated to improve patient care.

Introduction

Spinal cord tumours can occur in the parenchyma of the cord (intramedullary lesions), in the thecal sac but external to the cord (extramedullary lesions), or outside of the thecal sac (extradural lesions). Symptoms related to tumour growth vary depending on tumour location, and include myelopathy, numbness, loss of pain and temperature sensation, and radiculopathy if the tumour encroaches on nerve roots as they exit the spinal canal. Surgical resection combined with radiotherapy is the treatment of choice for most patients with spinal cord tumours, as no significant improvement in survival has been observed with

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chemotherapy alone in small cohort studies.[1–6] Given the limited efficacy of chemotherapy, rationally designed therapeutics for spinal cord tumours are urgently needed.

Intramedullary spinal cord tumours (IMSCTs) in adult patients account for only 5–10% of all spinal tumours, but are the most common spinal tumour in children.[7] Approximately 850–1,700 cases of IMSCT are diagnosed annually in adults, with astrocytomas, ependymomas and haemangioblastomas comprising the majority of intra-medullary lesions.[5] Ependymomas are the most common spinal lesions in adults, and occur in the cervical and thoracic cord or in the filum terminale.[8–10] Astrocytomas in the spinal cord comprise about 40% of all IMSCTs, but only 3% of CNS astrocytomas.[5,7] Astrocytomas and ependymomas most commonly affect patients with the neurocutaneous syndromes neurofibromatosis type 1 (NF1) and NF2, respectively.[7,11–17]

NF1 and NF2 have an autosomal dominant pattern of inheritance and no known risk factors. NF1 affects 1 in 3,000 people worldwide, whereas the prevalence of NF2 is approximately 1 in every 40,000–60,000 people.[18,19] Patients with neurofibromatosis are at an increased risk of developing various lesions including IMSCTs, and mutations in the *NF1* and *NF2* genes have been isolated in sporadic IMSCTs.[11,13,14,18,20,21] NF1 is a completely penetrant genetic disorder characterized by the presence of café-au-lait spots, axillary freckling, Lisch nodules on the iris, and nodular or plexiform neurofibromas that may lie beneath the skin or in deep tissue along peripheral nerves. NF2 is associated with bilateral vestibular schwannomas and the presence of a spinal cord lesion such as an ependymoma or meningioma.[18]

Haemangioblastomas are the third most common intramedullary lesion, and some of these tumours are associated with von Hippel–Lindau (VHL) disease—a disorder that leads to abnormal tumour growth in various regions of the body. 10–30% of patients with VHL disease present with haemangioblastoma in the spinal cord.[5,22] Haemangioblastomas are most commonly treated with radiotherapy or surgery but, owing to their hypervascular nature, the efficacy of angiogenesis inhibitors in these lesions is currently under investigation.[1,6]

Intradural extramedullary spinal cord lesions include meningiomas, neurofibromas and schwannomas. Meningiomas are benign lesions that constitute 25% of all spinal cord tumours and occur at high frequency in patients with NF2.[18,19] Schwannomas are nerve sheath tumours that occur sporadically and can also be associated with NF2. These lesions frequently occur at the dorsal root and can arise within the intradural space.[18] Neurofibromas are benign tumours of the PNS that comprise multiple cell types and are the hallmark of NF1.[19,23] Notably, plexiform neurofibromas can progress to become malignant peripheral nerve sheath tumours.

In this Review, we describe the genetics of spinal ependymomas, astrocytomas, haemangioblastomas, and meningiomas—the most common spinal cord tumours that are frequently encountered in clinical practice. Emerging targeted therapies for spinal cord tumours, which are in clinical trials for most of these pathologies, are also discussed. We highlight the lack of evidence for generalizability of intracranial tumour genetics to their

spinal counterparts, particularly in the case of ependymoma. Research to improve our knowledge of the genetic differences between spinal and intracranial tumour subtypes will be critical in guiding novel diagnostic and therapeutic strategies for patients with spinal cord tumours.

Intramedullary tumours

Astrocytomas

Demographics—Astrocytomas are the most common IMSCT in children, and the second most common in adults.[5,24,25] These lesions present as diffuse, heterogeneously enhancing masses in the parenchyma of the spinal cord (Figure 1). The WHO characterizes astrocytomas into four grades: pilocytic (grade I), diffuse or low grade (grade II), anaplastic (grade III) and glioblastoma (grade IV). Of note, pilocytic astrocytoma is clinically distinct from the grade II–III–IV spectrum of astrocytoma, and this type of astrocytoma predominates in children and adolescents.[7] By contrast, astrocytomas in adults are more likely to be of the diffuse type.[7]

Glioblastoma multiforme (GBM) in the spinal column is aggressive, resistant to chemotherapeutic intervention, and has the worst prognosis of spinal cord astrocytomas.[26–29] Primary glioblastomas, or *de novo* GBMs, are the most common malignant tumour in the brain but are rare in the spinal cord. Advances in our understanding of brain GBM biology, however, have provided useful information for investigations into astrocytoma tumourigenesis and progression in the spinal cord.[26,30]

Genetics—Genomic studies dedicated exclusively to spinal astrocytoma are limited owing to the rarity of this lesion, the small size of the tumour (which limits availability of tissue for research purposes), and the risks of complications associated with surgical resection of infiltrative spinal cord tumours. Such complications include worsening of neurological deficit, paralysis, bowel and/ or bladder dysfunction, and death. Studies into the genetics of intracranial astrocytoma have paved the way to identification of candidate genes for spinal astrocytoma tumourigenesis (Table 1) and revealed the central role of *BRAF* and isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* genes.[27,31–37]

BRAF is a proto-oncogene that regulates cell growth and has been implicated in various tumour types. Fusion variants of the serine–threonine protein kinase *BRAF* have been reported in gliomas of the CNS. In the spinal cord, *BRAF–KIAA1549* fusion genes are common in pilocytic astrocytomas[33,37,38] (reported in up to 75% of these tumours, although this value was based only on small studies[39]). In addition, the canonical Val600Glu *BRAF* mutation has been found in a variety of low-grade astrocytomas including pleomorphic xanthoastrocytoma.[32,35,38]

Approximately 68% of intracranial astrocytomas and 12% of glioblastomas demonstrate mutations in *IDH1* and/or *IDH2*.[26,40] Mutations in the *IDH* gene promote tumourigenesis via disruption of α-ketoglutarate production and subsequent abnormal production of 2-hydroxyglutarate[31]—a metabolite that competitively inhibits multiple histone demethylases—resulting in abnormal DNA methylation. This sequence of events is a clear example of

how one genetic alteration can have widespread epigenetic consequences. The rate of *IDH* mutations in spinal astrocytoma are not fully understood, but their frequency in spinal cord lesions is likely to be low given that most spinal astrocytomas occur in children, a population in whom *IDH* mutations are infrequent.[37]

Beyond these common mutations in astrocytoma, studies of spinal cord tumours have identified additional genes of interest. An analysis of nine cases of pilocytic astrocytomas revealed deletion of the tumour-suppressor gene cyclin-dependent kinase inhibitor 2A (*CDKN2A*; also known as p16) as the most common mutation.[34] This study also found loss of heterozygosity (LOH) at 9p21 (which encompasses *CDKN2A*), or at 10q23 (which encompasses the phosphatase and tensin homologue gene), in 31.6% and 50.0% of pilocytic astrocytomas, respectively.[34]

Pilocytic and high-grade intramedullary astrocytomas have also been reported in association with familial NF1.[41–43] Patients with NF1 have a mutation in the neurofibromin gene (17q11.2) that causes abnormal replication of nonmyelinating Schwann cells in the PNS. LOH of the *NF1* gene was observed in 92% of pilocytic astrocytomas in patients with familial NF1 compared with only 4% of those in patients without NF1.[13] Of note, however, only one case of definite spinal pilocytic astrocytoma was included in this cohort.

Data on intramedullary glioblastomas are scarce. Segmental loss of chromosome 8 has been described in one isolated case of paediatric spinal glioblastoma,[44] whereas a histopathological and immunohistochemical study of six spinal GBMs revealed that five were immunoreactive for tumour suppressor protein 53 (TP53).[45] Up to 60% of all diffuse astrocytomas have mutation of the *TP53* gene, but further studies are needed to determine whether this mutation is as common in spinal astrocytoma.[40]

Two landmark papers, published in 2012, reported high frequency of alterations in the gene encoding the replication-independent histone 3 variant H3.3 (*H3F3A*) in paediatric glioblastoma, which implicated abnormal DNA methylation in the generation of intracranial and spinal astrocytoma.[28,46] H3.3 is evolutionarily conserved throughout eukaryotes; however, two recurrent mutations (Lys27Met and Gly34Arg) in *H3F3A* were identified in 20–30% of nonbrainstem glioblastomas and nearly 80% of brainstem glioblastomas.[28,46,47] The H3.3 amino acid residue Lys27 is also known to be abnormally methylated in the setting of mutant *IDH1*, further highlighting the importance of the H3.3 variant and abnormal DNA methlyation in CNS tumourigenesis.[27,31]

Interestingly, mutations in the *ATRX* (α-thalassaemia/mental retardation syndrome X-linked) gene were linked to *IDH1* mutations in diffuse nonpilocytic astro-cytomas and secondary GBM in a cohort of 363 patients with brain tumours.[48,49] The *ATRX* gene regulates incorporation of H3.3 into telomeres and, therefore, has a critical role in chromatin remodelling and genomic stability.[48] Further research revealed that the H3.3 Lys27 mutation is the defining mutation of an epigenetic and biological subgroup of GBM that is characterized by proneural methylation, decreased expression of the gene encoding forkhead box protein G1 (a transcription factor involved in neuron growth and survival), younger patient age, and midline or spinal location.[27] The exact frequency of *H3F3A* mutations in

spinal cord GBMs remains to be elucidated, but emerging data suggest that intramedullary GBMs also have recurrent mutations in *H3F3A*.[27]

Treatment—Treatment of spinal astrocytoma in a symptomatic patient generally involves surgery (biopsy or resection) with or without radiation. In a review of surgical and adjuvant therapies for intramedullary lesions, Harrop and colleagues found that only low-quality evidence, in the form of case series, exists to guide clinical decision-making in patients with IMSCTs.[50] Surgical resection is beneficial in patients with pilocytic astrocytoma, especially when surgery is performed prior to onset of severe neurological decline (Figure 1).[50] High-grade lesions (WHO grade III and IV) are associated with a worse prognosis and have poorly demarcated boundaries for surgical resection. For these tumours, no significant survival benefit of aggressive surgical debulking has been reported, with 6-month mortality reported to be as high as 70%.[5,51] Even with low-grade astrocytoma (WHO grade II), gross total resection is achieved in as few as 12% of tumours.[52]

Postoperative radiotherapy for low grade intramedullary astrocytoma is associated with 5-year survival rates of 60–90%.[50] Adjuvant spinal radiotherapy has been advocated for patients who undergo biopsy only, for those with WHO grade II, III and IV lesions, and for those with advanced, progressive disease.[5,50] In one series of 22 adult patients with recurrent spinal cord astrocytoma, treatment with temozolomide (TMZ) was associated with an overall survival rate of 23 months.[2] Radiographical and clinical response rates of 37% have been reported with TMZ treatment in high-grade spinal cord astrocytoma.[53] Chemotherapy in pilocytic astrocytomas of childhood has demonstrated variable efficacy.[5]

For GBMs, vascular endothelial growth factor (VEGF) inhibition with bevacizumab is the only targeted therapy that is currently approved by the FDA, and attempts to inhibit the epidermal growth factor receptor pathway have yet to translate to improved outcomes.[54,55] Clinical trials of multikinase inhibitors, including cediranib, sunitinib and pazopanib, have uncovered drug-associated toxicities, with minimal or no improvement in patient survival.[56–59] Drugs that target heat-shock proteins and proteasome inhibitors are also under investigation in recurrent GBM.[54]

Ependymomas

Demographics—Ependymomas are the most common IMSCT in adults.[7,60] These lesions are thought to arise from ependymal cells of the central canal, but emerging evidence suggests that these tumours have similar histopathology to radial glial stem cells that have undergone malignant transformation.[61–64] In children, 90% of ependymomas occur intracranially, but when they arise in the spinal cord these tumours are often of the myxopapillary variant, originating from the filum terminale or conus medullaris.[7,8,10,65] In adults, 60% of ependymomas occur at either end of the spine—in the cervical spine, or in filum terminale as the myxopapillay variant.[66]

Ependymomas present as a centrally located mass in the spinal cord, grow slowly and have clearly demarcated borders (Figure 2). The WHO classifies ependymomas as subependymoma or myxopapillary (grade I), ependymoma (grade II) or anaplastic (grade III). Dissemination to the cerebrospinal fluid is considerably more likely with myxopapillary

ependymomas than with other forms of ependymomas, and can be evident even at presentation.[67] Subependymomas are slow growing and less common in the spinal cord than are other ependymomas (Figure 2).

Genetics—Childhood and adult ependymomas are distinct clinical entities, and emerging evidence suggests that they arise from biologically distinct stem cell precursors.[64] In a cross-species comparison of mouse and human ependymoma transcriptomes, human supratentorial ependymomas bore transcriptomic similarities to embryonic cerebral neural stem cells (NSCs) from mice that were deficient in *CDKN2A*, which is conserved between humans and mice and, as mentioned above, is a tumour-suppressor gene. Human spinal cord ependymoma cells, however, resembled adult mouse NSCs.[64] This genetic signature reflects the clinical phenotype, with spinal ependymomas being more common in adults, and childhood ependymoma arising primarily in the intracranial compartment. Notably, however, this study has major limitations as the researchers drew conclusions on the basis of findings from a genetically modified mouse model and the investigation involved comparison of tissues from different species.

Studies of ependymoma genetics often include both spinal and intracranial cohorts (Table 2), but substantial evidence suggests that spinal ependymomas are genetically distinct from their cerebral counterparts.[65,68,69] Application of consensus hierarchical clustering and non-negative matrix factorization to two nonoverlapping databases of grossly histologically similar ependymoma tissues enabled identification of three distinct groups of tumours on the basis of their localization—namely, supratentorial, posterior fossa and posterior fossa with spine.[70] The spinal ependymomas clustered with a distinct subgroup of posterior fossa ependymomas, and demonstrated whole-chromosome anomalies, as well as mutations affecting the ciliogenesis, microtubule assembly, and mitochondrial and oxidative metabolism pathways.[70] These robust results were replicated on multiple subgroup analyses.

Analysis of RNA expression in newly diagnosed lesions found overexpression of genes encoding homeobox B5 (*HOXB5*), phospholipase A2 group 5 (*PLA2G5*) and inter-α-trypsin inhibitor heavy chain 2 (*ITIH2*) in four of four grade I spinal ependymomas and three of six grade II spinal ependymomas.[69] In an RNA microarray-based correspondence analysis, the *HOX* family of genes was further implicated in extracranial ependymoma development.[65] This study included 14 spinal ependymomas but, notably, the researchers did not specify whether tumours in the extracranial cluster involved brainstem as well as spinal cord tumours.[65] *HOXB5* is a transcription factor implicated in lung and gut development, but in one study this gene was found to have a role in migration of neural crest cells and was associated with acute myeloid leukaemia and oesophageal neoplasms.[69] In a larger study that used comparative genomic hybridization in 122 patients with intracranial ependymoma, poor prognosis was associated with amplification of chromosome 1q and homozygous deletion of *CDKN2A*.[71]

Further highlighting the heterogeneity of spinal and intracranial ependymomas, mutations in the *NF2* gene are found almost exclusively within spinal cord ependymomas.[21] Homozygous deletion, LOH and mutations in the *NF2* gene have been found in both sporadic and NF2-associated spinal ependymomas, and monosomy or alteration of

chromosome 22q is observed in 30% and 40% of spinal ependymomas, respectively.[65,68,72] The *NF2* gene is located on chromosome 22q12 and encodes the scaffolding protein merlin, also known as schwannomin. Merlin is a moesin–ezrin–radixin-like protein and is part of the 4.1 family of transmembrane-to-actin cytoskeleton linker proteins.[73] In familial NF2 and various human cancers, abnormalities in the merlin protein prevents cells from responding to contact inhibition, leading to dysregulation of cell growth and proliferation.[73,74]

Treatment—Spinal cord ependymomas display variable growth characteristics, and treatment is dictated by the degree of cord compression and symptoms.[20] Surgery is appropriate for symptomatic patients, and treatment with adjuvant radiation led to 10-year survival of 50–100% in reported cases.[50] The effects of adjuvant chemotherapy, specifically etoposide and carboplatin, have been described in a few case reports and case cohorts in which the choice of agent used to treat the spinal cord lesion was determined by the treatment used for intracranial ependymoma.[4] In a study of 10 patients with recurrent intramedullary ependymoma who were treated with etoposide, two experienced a partial response and five patients showed stabilization of disease following one cycle of drug administration.[4] Another trial involving 25 patients with recurrent spinal ependymoma found no beneficial response to chemotherapy in patients who had failed a platinum-based regimen. The use of targeted therapeutics in spinal cord ependymomas has not been well-described; however, in one case in which the tumour expressed platelet-derived growth factor (PDGF) receptor, tumour regression was reported following administration of imatinib—a drug that targets the PDGF-β receptor.[75]

Haemangioblastoma

Demographics—Spinal cord haemangioblastomas are rare, benign, vascular lesions that can occur sporadically or as a manifestation of VHL disease (Figure 3). When these tumours arise in the spinal cord, bleeding can cause neurological impairment owing to the formation of space-occupying haematomas. Approximately 20–30% of haemangioblastomas occur in association with VHL disease, and they are also part of the clinical presentation of retinal angioma, renal cysts, pheochromocytoma, endolymphatic tumours and epididymal cystadenoma.[22,76] VHL disease has an autosomal dominant inheritance pattern with 90% penetrance, and is caused by loss of the tumour suppressor gene located at 3p25–26. When the *VHL* gene is mutated or absent, cells constitutively express hypoxia inducible factors (HIFs), which stimulates the growth of new blood vessels.[22,76,77]

Genetics—The *VHL* gene encodes the substrate-binding subunit of the E3 ubiquitin ligase that degrades HIF-α—a transcription factor that regulates glucose transport, glycolysis, erythropoeisis and angiogenesis. When the *VHL* gene is mutated or absent, cells cannot target HIF-α for poly-ubiquitination and degradation.[22,76,77] Constitutively active HIF-α causes proliferation of blood vessels and growth of benign vascular lesions.[78] In a review of *VHL* gene functions, Bader and colleagues reported that *VHL*-mutant cells secrete high levels of growth factors including VEGF, transforming growth factor-β, PDGF-β and tumour necrosis factor-α.[78] These findings highlight the role of *VHL* as a multifaceted tumour-suppressor gene.

In VHL-associated tumours, 94% express germline mutations in the *VHL* gene, and 62% exhibit LOH at the VHL locus. By contrast, only about 20% of sporadic lesions have mutations in *VHL* and 50% have LOH of the VHL locus.[22,76,79] As with most other hereditary cancer syndromes, haemangioblastoma formation in patients with VHL disease probably occurs via the 'two-hit' mechanism, whereby patients harbour the germline mutation and also undergo a second somatic mutation, which results in biallelic inactivation.[79] Diverse genetic aberrations have been uncovered in sporadic haemangioblastomas, with LOH at 22q13 and 3p21-23 found in subsets of individuals with haemangioblastomas without VHL disease.[80] In a study of the cytogenetic profiles of haemangioblastomas, loss of chromosome 19, 6 or 22q was observed in 35%, 30% and 15% of samples, respectively.[81]

Treatment—Spinal cord haemangioblastomas are common in patients with VHL disease, and early MRI screening is recommended from age 10 in individuals with this disorder.[77] Surgery has shown benefit both in patients with VHL-associated haemangioblastoma and in those with sporadic haemangioblastoma,[82] and is recommended when the tumour becomes symptomatic and the patient experiences weakness, pain or difficulty walking. For individuals with asymptomatic lesions, serial MRI and clinical monitoring are recommended. Preoperative angiography can assist the surgeon in planning and diagnosis. Embolization is rarely performed, however, owing to the risk of ischaemic injury in the adjacent spinal cord parenchyma.

Anatomically, haemangioblastomas of the spinal cord arise from the pial layer and are considered juxta-medullary, but can exhibit an encapsulated, intra-medullary component (Figure 3).[83] Surgical resection of spinal haemangioblastoma is complicated by the risk of bleeding and local ischaemia during surgery. Complete resection is possible with the use of microsurgical techniques,[83] and radiosurgery is a less invasive option for local tumour control.[84] In small case series, antiangiogenic therapy with SU5416 (an inhibitor of VEGF receptors) and thalidomide led to stabilization of disease.[85,86] Bevacizumab, a pan-VEGF inhibitor, has been used to successfully treat retinal haemangioblastomas in patients with VHL.[87]

Extramedullary intradural tumours

Meningiomas

Demographics—Spinal meningiomas are extramedullary intradural tumours arising from the meningothelial cells that reside within the leptomeninges of the spinal cord. These lesions account for 25% of all spinal tumours and comprise a diverse array of histologically distinct subtypes, including angiomatous, fibrous, meningothelial, metaplastic, psammomatous, transitional, atypical and clear-cell variants.[30] Psammomatous, meningothelial and transitional meningioma are most commonly reported in the spine,[88,89] and although these tumours are usually benign, they can cause substantial spinal cord compression (Figure 4). Surgical resection with adjuvant radiation is often the first line of treatment and is recommended in cases in which disease is persistent or recurrent.[90] Meningiomas often manifest in the thoracic spine and are most common in female patients and in the fourth and fifth decade of life.[90,91] Unlike their intracranial counterparts, spinal

meningiomas are unlikely to recur after surgical resection, with recurrence rates of 0–13% reported.[24,88,92–94]

Genetics—Chromosome 22q deletion and consequent loss of the gene is the most consistently described genetic abnormality associated with spinal meningiomas (Table 3).[90,95–99] In a microarray-based study of spinal and intracranial meningiomas, Sayagues and colleagues reported that homozygous chromosome 22 deletions were more likely to be associated with spinal than with intracranial meningiomas, and lesions isolated from the spine were likely to originate from a single-cell clone.[100]

Homozygous deletion of the *NF2* gene is evident in up to 80% of nonfamilial meningiomas and in 100% patients with NF2 and spinal meningioma.[99] In a study of 16 cases of spinal meningioma, half of all patients had complete or partial deletion of chromosome 22q, and this mutation was associated with a more-aggressive anaplastic or atypical phenotype.[101] LOH of DAL-1 (differentially expressed in adenocarcinoma of the lung, also known as EPB41L3) which, like merlin, is a member of the protein 4.1 family, has been found in up to 60% of sporadic meningiomas.[95,96,102] In these studies, however, whether the mutation was found specifically in spinal meningiomas was not discussed.

The balance between overexpression and inhibition of matrix metalloproteinases (MMPs) has also been implicated in regulation of spinal meningioma growth and invasion.[103–105] In a study of 58 spinal meningiomas, MMP-9 expression was identified in 73% of cases, and high levels of expression were observed in 46%.[91] Immunoblot analysis has revealed low levels of tissue inhibitors of metalloproteinases 1 and 2 in multiple meningioma phenotypes.[96,102,104] Of note, these studies did not specify whether spinal meningiomas were included in the analysis and, therefore, the role of tissue inhibitors of metalloproteinases in spinal tumourigenesis remains to be determined.

In addition to the genes described above, many genomic alterations have been reported in intracranial meningiomas. Mutations in chromosome 9 at the *CDKN2A–CDKN2B* locus were identified as the most frequent mutation in meningiomas that progressed from grade II to grade III.[105] The hedgehog signalling pathway has also been implicated in this transition: compared with high-grade meningiomas, low-grade meningiomas overexpressed several hedgehog pathway-related genes and had lower levels of transcripts of the gene that encodes protein patched homolog 1—a key ligand in the hedgehog pathway.[95,106] Future research will be necessary to determine whether such intracranial mutations are also common to spinal meningioma.

Treatment—Whereas meningiomas are classically benign lesions with a good prognosis, patients with NF2 and a meningioma constitute a high-risk population who should be monitored closely for detection of distant and local recurrence of spinal tumours.[107–109] The value of chemotherapy in meningioma is limited owing to the low mitotic activity of the tumour cells, and no effective therapy for meningioma following incomplete surgical resection is available. *In vitro* studies have demonstrated that the drug trabectedin exerts anti-meningioma activity via inhibition of angiogenesis.[110] Trabectedin was tested in one patient with anaplastic intracranial meningioma and led to some radiographical response, but

the study was terminated owing to drug toxicity in the fifth cycle of drug administration.[110] AR-42, a histone deactylase inhibitor, has been tested *in vitro* and demonstrated marked antiapoptotic activity. A phase I trial of AR-42 is currently under way for patients with NF2 and meningioma.[111] Everolimus, an mTOR inhibitor, is currently in phase II trials for patients with NF2 and meningioma,[112] and two trials of PDGFR inhibitors, namely valatinib and sunitinib, are also ongoing.[112]

Conclusions and future directions

Recent advances have highlighted the unique genetic expression profiles of spinal haemangioblastoma and ependymoma, but much work remains to be done to understand differences between intracranial and spinal astrocytomas and meningiomas. By contrast, spinal astrocytomas are not substantially different from their supratentorial counterparts. Some evidence suggests that genetic alterations within spinal astrocytoma cohorts are more limited than in intracranial astrocytoma cohorts. One explanation for this phenomenon is that spinal astrocytomas become symptomatic at a smaller size than do intracranial lesions and, thus, become clinically apparent at an earlier stage. Consequently, spinal astrocytomas may not have time to accumulate as many genetic mutations as tumours that arise in noneloquent regions of CNS. The intracranial tumours would, therefore, present at a later stage of disease and would be much larger than spinal astrocytomas. This same logic may also apply to spinal and intracranial meningiomas.

For intracranial tumours, some targeted therapies have shown benefit, but such treatments may not be applicable to spinal tumour cohorts owing to the variable—or altogether different—genetic profile of spinal tumours compared with brain tumours. Clinical trials of targeted therapies in spinal tumour cohorts are, unfortunately, also limited owing to the rarity of spinal IMSCTs. Multi-institutional, multinational clinical trials are critically needed to enrol sufficient numbers of patients for comparisons between investigational drugs to reach statistical significance, and to enable research in spinal cord tumours to progress towards novel treatments.

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Review criteria

Articles indexed in PubMed, published after 1983, written in English, and concerning basic, translational or clinical studies of CNS tumours of the brain or spine were considered for inclusion. Search terms included “genetics AND spinal cord tumours”; “intramedullary spinal cord tumours”; “ependymoma genetics”; “astrocytoma AND spine”; “astrocytoma AND genetics”; and “haemangioblastoma AND genetics”. Articles were included only if full abstracts were available. Full-text papers were reviewed when available. The reference lists of identified papers were then searched for additional primary articles.

Key points

- Familial neurofibromatosis type 1 is associated with spinal astrocytoma and neurofibromas, whereas familial neurofibromatosis type 2 (NF2) is associated with spinal ependymoma and meningioma
- von Hippel–Lindau (VHL) disease and mutations in the *VHL* gene are associated with spinal haemangioblastoma
- Mutations in the gene encoding the histone 3 variant H3.3 (*H3F3A*) and in the fusion gene *BRAF–KIAA1549* are evident in spinal astrocytomas
- The genes associated with ependymoma (including mutations in *NF2*, *HOXB5* and *PLAG2*) are heterogeneous, varying according to histological subtype, tumour location and patient age
- Genes encoding protein 4.1 family members *NF2* and *DAL-1*, members of the Hedgehog signalling pathway, matrix metalloproteinase-9, and tissue inhibitors of metalloproteinases, have been implicated in meningioma
- Surgical resection and adjuvant radiotherapy remain the primary treatment modalities for spinal cord tumours, and targeted therapeutics are under investigation

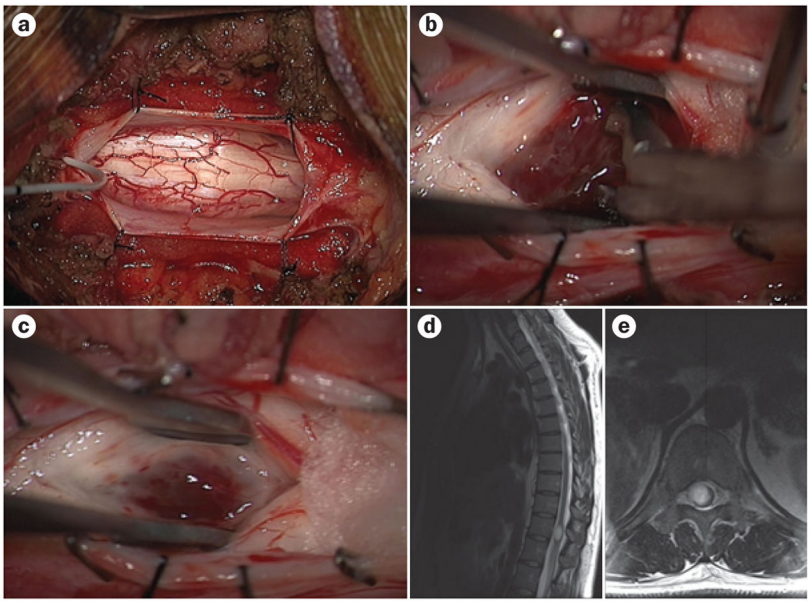

Figure 1.

Surgery and imaging in spinal cord astrocytoma. **a**–**c** | Intraoperative images showing the excision of a diffuse intramedullary astrocytoma in the spinal cord from a posterior approach. The spinal cord appears enlarged, and the surgical approach begins with a midline myelotomy to separate the dorsal columns (a). The tumour is then exposed and excised via careful dissection (b). Gliosis and hyperaemia can be seen in the resection cavity (c). **d**, **e** | Preoperative sagittal (d) and axial (e) T2-weighted MRI reveal hyperintensity and expansion of the spinal cord.

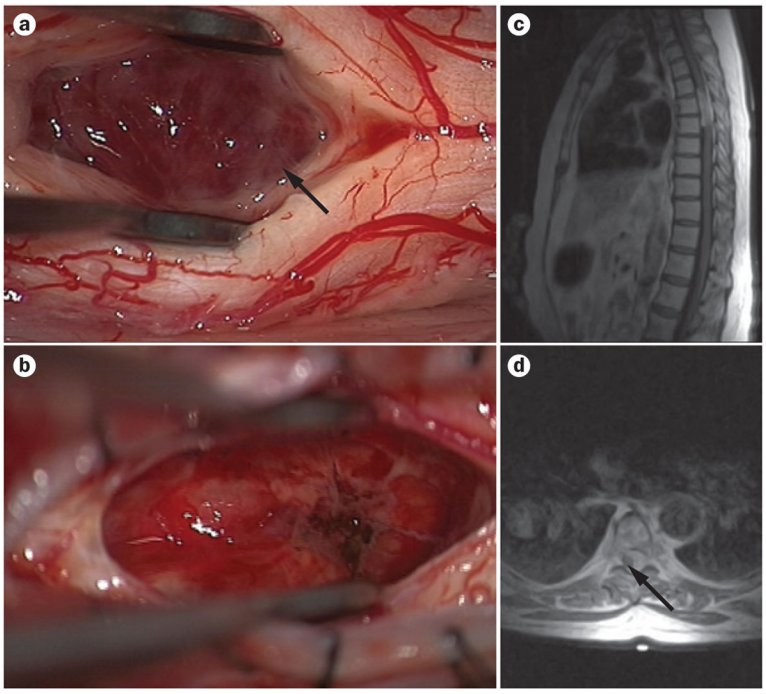

Figure 2.

Surgery and imaging in spinal cord ependymoma. **a**, **b** | Intraoperative pictures show the tan-coloured tissue that is often seen with ependymomas (arrow; a), and a resection cavity after tumour removal (b). **c**, **d** | Preoperative sagittal (c) and axial (d) T2-weighted MRI of thoracic ependymoma demonstrating a space-occupying lesion that is hyperintense to the cord in the thoracic spine. The lesion causes marked cord displacement on axial view; the cord can be seen as a hypointense sliver of tissue (arrow; d).

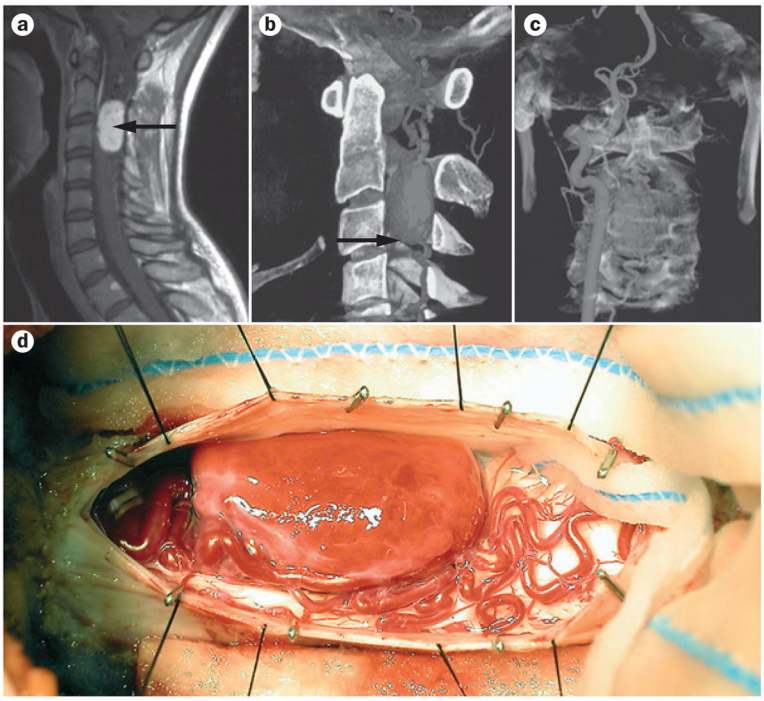

Figure 3.

Surgical and preoperative imaging of haemangioblastoma in the cervical spine. **a** | Sagittal postcontrast T1-weighted MRI shows a well-defined lesion (arrow) in the spinal cord at C2–C3. **b** | 3D CT angiogram reconstruction demonstrating a large vascular lesion (arrow). **c** | As haemangioblastomas are richly vascular, direct arterial injection can facilitate preoperative imaging, surgical planning, and preoperative embolization. Image depicts filling of ipsilateral vertebral artery and subsequent tumour filling. **d** | Intraoperative image of haemangioblastoma. Permission obtained from American Association of Neurological Surgeons © Sciubba, D. M. *et al. J. Neurosurg. Spine* **5**, 96–100 (2006).

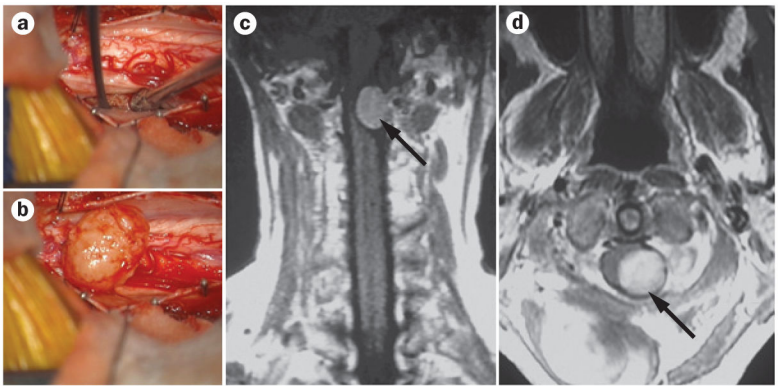

Figure 4.

Surgery and imaging of spinal cord meningioma. **a**, **b** | Intraoperative images showing pre-exposure (a) and postexposure (b) of a spinal meningioma. **c**, **d** | Coronal (c) and axial (d) postgadolinium MRI demonstrating a cervical extramedullary meningioma (arrows) with avid enhancement.

Table 1

Genetic mutations associated with astrocytoma

Locus	Gene	Tumour location	Tumour grade or type	Study details and/or findings
7q34	*BRAF*	Spinal cord and brain	Pilocytic astrocytomas	Eight paediatric spine pilocytic astrocytomas[39]
9q21	*CDKN2A*	Spinal cord and brain	Pilocytic astrocytomas	147 pilocytic astrocytomas, including nine spinal cases[34]
17q25	*H3F3A*	Spinal cord and brain	GBM	H3.3 gene identi ed as epigenetic marker of midline or spinal GBM[27,28,46,47]
2q33.3	*IDH1*	Brain > spinal cord	Intracranial astrocytoma and glioblastoma	Immunohistochemical evidence of tumour in spine; well-established as cranial tumour[27,31,46,47]
17q11.2	*NF1*	Brain > spinal cord	Pilocytic astrocytomas	37 pilocytic astrocytomas, including one spinal case[13]
17p13.1	*TP53*	Brain	Diffuse astrocytoma	Mutation evident in 60% of patients with astrocytomas[30,41,113]
Xq21.1	*ATRX*	Brain	All astrocytoma	Associated with *IDH1* in study of 363 brain tumours[48]
10q23.3	*PTEN*	Unspecified	Pilocytic astrocytomas	147 pilocytic astrocytomas, including nine spinal cases[34,35]

Abbreviations: *ATRX*, α-thalassaemia/mental retardation syndrome X-linked; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; GBM, glioblastoma multiforme; *H3F3A*, histone 3 variant H3.3; *IDH1*, isocitrate dehydrogenase 1; *NF1*, neurofibromatosis type 1; *PTEN*, phosphatase and tensin homologue; *TP53*, tumour suppressor protein 53.

Table 2

Genetic mutations associated with ependymoma

Locus	Gene	Tumour location	Tumour grade or type	Study details
17q21.3	*HOXB5*	Spinal cord	Grade II–III	39 ependymomas, including 10 spinal samples[69]
1p35	*PLA2G5*	Spinal cord	Grade II	39 ependymomas, including 10 spinal samples[69]
10p15	*ITIH2*	Spinal cord	Grade II	39 ependymomas, including 10 spinal samples[69]
22q12	*NF2*	Spinal cord	Sporadic and NF2-associated Grade II–III	27ependymomas, including 15 spinal samples[68]
9q21	*CDKN2A*	Brain	Grade II and III	122 intracranial ependymomas[71]
1q	Multiple	Brain	Grade II and III	122 intracranial ependymomas[71]

Abbreviations: *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *HOXB5*, homeobox 5; *ITIH2*; inter-α-trypsin inhibitor heavy chain 2; NF2, neurofibromatosis type 2; *PLA2G5*; phospholipase A2 group 5.

Table 3

Genetic mutations associated with meningioma and haemangioblastoma

Locus	Gene	Tumour location	Tumour grade or type	Study details
22q12	*NF2*	Spinal cord	All meningiomas	16 spinal meningiomas[101]
20q11.2	*MMP9*	Spinal cord	All meningiomas	58 spinal meningiomas[91]
9q21	*CDKN2A*	Brain > spinal cord	Grade III	36 paired samples (18 patients)[106]
Multiple	Hedgehog pathway*	Brain	All meningiomas	36 intracranial meningiomas[108]
10p11.32	*DAL-1*	Unspecified	Malignant meningiomas	63 sporadic meningiomas, locations unspecified[96]
22q13.1	*TIMP*	Unspecified	All meningiomas	30 meningiomas[91]
3p25-26	*VHL*	Spinal cord	Sporadic and VHL-associated haemangioblastoma	45 spinal haemangioblastomas[76]

* Multiple members of the hedgehog signalling pathway are involved.

Abbreviations: *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *DAL-1*, differentially expressed in adenocarcinoma of the lung; *MMP9*, matrix metalloproteinase 9; *NF2*, neurofibromatosis type 2; *TIMP*, tissue inhibitor of metalloproteinase; VHL, von Hippel–Lindau.