

Pineoblastoma in a child with 22q11.2 deletion syndrome

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DESCRIPTION

A 4-year-old girl with a history of chromosome 22q11.2 deletion syndrome presented to the emergency department with 2–3 weeks of worsening emesis. CT of the head revealed a large pineal region calcified tumour with associated hydrocephalus. Contrast-enhanced MRI of the brain and spine status postexternal ventricular drain placement confirmed a pineal tumour with diffuse metastatic leptomeningeal spinal spread (figure 1A,B). The child had a normal MRI of the brain 2 years prior (figure 1C) as work-up for her developmental delay. The diagnosis of 22q11.2 deletion syndrome was made by chromosomal microarray testing, which revealed a 2.5 MB deletion of 22q11.2 that included the *TBX1* gene. Neuropathology on a subtotal resection showed clusters and sheets of tightly packed, small, blue cells with oval or slightly angulated nuclei and scant cytoplasm, consistent with a primitive neuroectodermal tumour. The tumour showed no loss of expression of INI that would be characteristic of atypical teratoid rhabdoid tumour. In the pineal region, the constellation of neuropathic features is diagnostic of a pineoblastoma. Next-generation sequencing assay of the tumour revealed no reportable genomic alterations. Specifically, there were no reported deletions, duplications or mutations in *SMARCB1*. Variants of unknown significance of five genes were reported (*AR*, *ARID1B*, *CARD11*, *FH* and *FLT1*). The patient was treated with high-dose craniospinal radiation and adjuvant chemotherapy; however, she died of progressive disease 1 year post-therapy.

22q11.2 deletion syndrome is the most common microdeletion syndrome, occurring in approximately 1 per 4000 births. It involves variable-sized

heterozygous deletions of regions of 22q11, resulting in a wide phenotypic spectrum that can include cardiac and palatal malformations, immune deficiency, endocrine, genitourinary and gastrointestinal problems, and neuropsychiatric disorders. Although still relatively rare, there are accumulating reports of malignancy in this patient population.^{1,2} Several reasons have been proposed for their increased risk of malignancy.^{1,2} These include thymic hypoplasia leading to a range of T-cell defects, and immune deficiency which predisposes to haematological malignancy due to aberrant immune surveillance; an increased frequency and/or severity of infections with possible involvement of carcinogenic viruses such as Epstein-Barr virus; repeated infections creating a state of chronic inflammation, which predisposes to malignancy; and the deletion generally involving the catechol-O-methyltransferase gene, which plays a role in detoxification of certain environmental carcinogens.

It is likely that 22q11.2 deletion syndrome is the key driver for the development of pineoblastoma in this patient. Pineoblastoma is an exceedingly rare malignant tumour, with an estimated incidence of <0.1% of all intracranial tumours.³ It typically presents with mass effect and obstructive hydrocephalus, and are rapidly growing and invasive. Known genetic alterations that predispose to pineoblastoma include germline mutations in *RB1* and *DICER1*.³ Treatment consists of surgery, radiotherapy and chemotherapy. This is the second case of pineoblastoma associated with 22q11.2 deletion syndrome² and the first case with a normal prior MRI.

Further studies are needed to determine the precise incidence and prevalence of malignancy

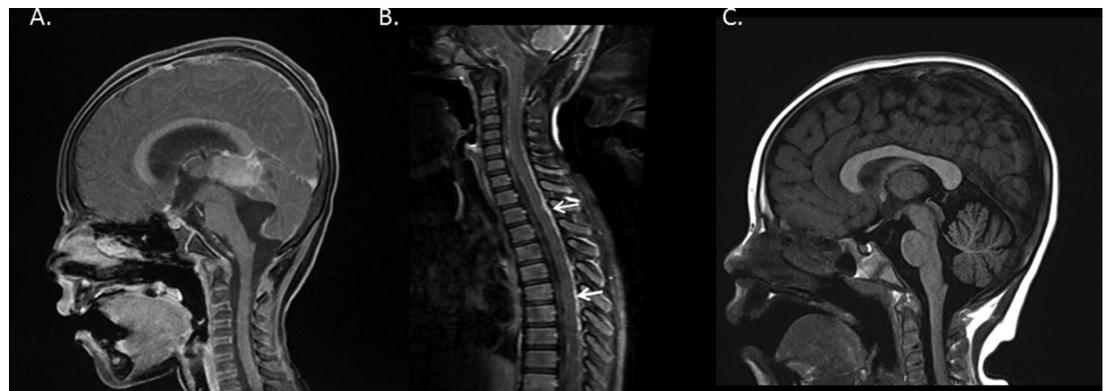


Figure 1 MRI of the brain and spine at presentation (A and B) shows a 3.2 mm pineal mass on T1 sagittal postcontrast (A) with diffuse leptomeningeal spinal spread (B, arrows). MRI of the brain 2 years prior was normal (C).



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Learning points

- ▶ 22q11.2 deletion syndrome may be associated with an increased risk of malignancy, including brain cancer.
- ▶ Brain tumours should be considered in the differential diagnosis when children with 22q11.2 deletion syndrome present with new-onset neurological signs/symptoms.

in association with 22q11.2 deletion syndrome and identify the mechanism by which this patient population may have an increased risk of malignancy. Our case highlights the importance of neuroimaging in patients with 22q11.2 deletion syndrome and illustrates the rapid growth velocity of the disease given the history of a normal MRI 2 years prior to diagnosis.

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