Challenges in the diagnosis of medulloblastoma recurrence at an unusual site in a patient with Prader-Willi syndrome

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ABSTRACT

Medulloblastoma is the most common malignant paediatric brain tumour. Survival rates range between 50-80% depending on histology and other biological features, metastases and treatment approach. Prader-Willi syndrome (PWS) is a genetically inherited disorder characterized by dysmorphic features, mental retardation, obesity and hypogonadism among other features. We describe a 10.5-year-old girl with PWS and previous standard-risk medulloblastoma that relapsed in the pons three years after the end of treatment. Diagnosis of relapse was delayed by a preceding varicella infection, an initial clinical/radiological response to steroids and the unusual location and was confirmed with a stereotactic biopsy. The patient did not respond to second-line treatment. This is the first report of a medulloblastoma in a patient with PWS

Key Words: medulloblastoma; Prader-Willi syndrome; relapse; varicella; pontine lesion; childhood cancer

Introduction

Medulloblastoma (MBL) is the most common malignant (WHO grade IV) brain tumour in children.[1] It belongs to the group of embryonal tumours. It can be further characterized histologically (classic, desmoplastic/nodular, with extensive nodularity, large cell/anaplastic) and genetically (WNT-activated, SHH-activated/TP53-mutant, SHH-activate/TP53-wild type, non-WNT/non-SHH (groups 3 and 4).[2] It is associated with several cancer predisposition conditions such as Fanconi anaemia and the Gorlin, Turcot, Li-Fraumeni, and Rubinstein-Taybi syndromes. The cancer predisposition genes *APC, BRCA2, PALB2, PTCH1, SUFU*, and *TP53* are suggested as medulloblastoma predisposition genes depending on the molecular subtype.[3]

It is by definition located in the posterior fossa and metastasizes within the neuraxis with 30% of patients having disseminated disease at diagnosis.[1] Treatment involves upfront surgical resection, radiotherapy and conventional or high-dose chemotherapy with autologous haematopoietic stem cell rescue.[4] Overall survival approaches 80% in standard-risk tumours and around 60% in high-risk patients.[5] Recurrence occurs in approximately 30% of patients, locally at the tumour bed, as distant leptomeningeal spread or as combined local and distant relapse.6 Secondary neoplasms are rare (<4%) and are usually related to the radiotherapy although cancer predisposition syndromes may play a role.[5] (Packer 2013)

Prader-Willi syndrome (PWS) is a genetic condition with an incidence between 1:15,000 to 1:30,000 live births.[7] It is characterized by hypothalamic dysfunction (lack of satiety and hyperphagia, obesity, short stature, hypogonadism, hypogenitalism, and cryptorchidism), as well as distinctive facial appearance, small hands and feet, learning difficulties and behavioural problems.[7] It is associated with

significant morbidity and mortality[7] including an increased incidence of malignant conditions. [8, 9]

We present a young patient with PWS and medulloblastoma in complete remission that recurred at an unusual site, three years after the end of treatment. To our knowledge, this is the first report of a medulloblastoma in a paediatric patient with PWS and the first report of medulloblastoma recurrence at the pons.

Case report

A 10.5-year-old girl with Prader-Willi syndrome presented with acute onset right-sided hemiplegia and left-sided facial nerve palsy associated with dysphagia and slurred speech. At the age of six years she had been treated for standard risk medulloblastoma (classic histology, *MYC/MYCN* not amplified, non-WNT/non-SHH activated (by immunohistochemistry), no metastases-M0) as per the HIT-SIOP PNET-4 trial.[10] More specifically, she underwent complete surgical resection followed by craniospinal radiotherapy (23.4 Gy) with posterior fossa boost (up to 54 Gy) and eight courses of chemotherapy (Packer protocol: Vincristine, Lomustine and Cisplatin). [11] The treatment was tolerated well without significant problems despite her underlying condition.

Three years after completion of treatment the patient had remained completely asymptomatic and free of disease on regular 6-monthly surveillance imaging. Three months after her last scan she presented with the above described acute neurological symptoms. Brain MRI (Figure 1, Panel A) showed a new, space-occupying, enhancing, coalescent nodule with restricted diffusion in the left aspect of the pons and medullary pyramid. The tumour bed and spine remained clear~~. Her latest brain and spine MRI had been performed three months earlier and were completely free of~~

~~disease~~. One week before the onset of these symptoms she had developed chickenpox. Vesicular fluid PCR was positive for Varicella-Zoster virus (VZV) and she was initially treated with oral acyclovir. Examination of the CSF was negative for malignant cells, bacterial or VZV infection and positive for Enterovirus (ECHO virus type 3), which was thought to be of no clinical significance. At that point, because of the temporal association with the varicella, the lesion was considered to represent a reactive, post-infectious process, and the patient was started on dexamethasone and high dose acyclovir intravenously. Her muscle strength, speech and swallowing gradually improved and a repeat MRI five days later showed significant reduction in the enhancement of the lesion (Figure 1, Panel B).

Acyclovir and dexamethasone were continued for two weeks. However, on weaning of dexamethasone symptoms gradually recurred whereas a blanching erythema of the fingers and purplish-red discoloration of the soles of the feet appeared. A full vasculitis screen was performed including magnetic resonance angiography (MRA) of the brain that was negative; however, the MRI reported a further increase in the size of the lesion with recurrence of the avid enhancement (Figure 1, Panel C). High dose dexamethasone was restarted with rapid clinical and radiological (Figure 2) response. To elucidate the nature of the lesion a technically challenging stereotactic biopsy was performed, which showed a tumour composed of pleomorphic anaplastic cells set in a myxoid stroma. The tumour cells showed strong reactivity for synaptophysin but were negative for GFAP, an immunophenotype strongly favouring recurrent medulloblastoma and arguing against a secondary glioma. There was no *MYC* or *MYCN* amplification and the immunophenotype favoured a non-WNT/non-SHH medulloblastoma. She was started on palliative chemotherapy with temozolomide 150 mg/m^2/day for 5 days along with celecoxib for

its known anti-inflammatory and antiangiogenic effect. Palliative radiotherapy was considered but deferred due to the size of the lesion, the high possibility of oedema that would cause obstruction of CSF flow and because of the worsening symptoms. Unfortunately, the patient deteriorated rapidly on day 5 of chemotherapy and died on day 7 of the first cycle.

Discussion

We have described a patient with Prader-Willi syndrome and successfully treated standard risk medulloblastoma that presented with a lesion in the pons three years after the end of treatment. The lesion had features of a recurrent medulloblastoma. This is the first report of medulloblastoma in a patient with Prader-Willi syndrome that additionally presented certain diagnostic and management challenges. Establishing a diagnosis was confounded by the following factors: 1) lesion location, 2) concurrent VZV infection, 3) clinical and radiological response to steroids, 4) lesion not easily accessible by biopsy, 5) association with Prader-Willi syndrome.

First, the location of the lesion was very atypical since relapses tend to be either local at the tumour bed, distant leptomeningeal metastases (most commonly) or combined.[12] The location of the lesion would be more consistent with a brainstem/pontine glioma like those reported after radiotherapy for MBL that require completely different management and have a very poor prognosis.[5] But most importantly, the pons can be the location of non-malignant lesions such as autoimmune processes.[13]

Second, the concurrence of the symptoms with varicella delayed the diagnosis as the lesion was initially considered to be associated with the infection. Although rare, there are reports of adult patients with pontine lesions associated with VZV

143 infection such as localized post-varicella encephalitis[14] or with auricular herpes
144 zoster.[15, 16] The negative VZV PCR of the CSF however did not support a causal
145 association with varicella. Interestingly, Enterovirus PCR was positive in the CSF but
146 was considered an incidental finding at the time. Two recent articles from Korea and
147 China reported immune mediated neurologic manifestations with MRI changes of the
148 brainstem related to infection with another Enterovirus 71, a neurotropic virus that
149 causes hand, foot and mouth disease.[17, 18]

150 Third, the steroid-induced change in the appearance of the lesion misled the
151 multidisciplinary team to believe that it might not be malignant. Steroids were
152 discontinued after symptoms and imaging improved. Weintraub *et al.*, have also
153 described a 10-year old girl with suspected relapsed medulloblastoma when she
154 presented with new clinical deficits and radiological evidence consistent with
155 recurrence.[19] In this case as well, both clinical and imaging findings completely
156 resolved after treatment with steroids. A definite diagnosis was not established.[19] The
157 case highlights the risks of assuming recurrence based on clinical and imaging
158 changes alone. In our patient, after a short-lived initial improvement both symptoms
159 and radiological findings worsened when the steroids were weaned. This led to the
160 decision to perform a biopsy to establish the exact nature of the lesion and exclude a
161 brainstem glioma or a lymphoma, which -although exceedingly rare especially in
162 young patients- could not be completely ruled out.

163 Fourth, biopsy of any brainstem lesion is a challenging procedure and
164 therefore diagnosis is usually based on its characteristics on imaging. Our patient's
165 past medical history, the concurrent conditions and the unusual behaviour of the
166 lesion dictated the performance of a stereotactic biopsy. The procedure was
167 uneventful and the patient fully recovered post-operatively. Biopsy of brainstem

lesions is increasingly becoming necessary as molecular information will be used to guide treatment decisions in the near future.

Finally, the possibility of an association with the underlying PWS was considered. Patients with PWS present increased morbidity and early mortality with a death rate of 3% per year. The most common complications of PWS are dementia and psychosis.[7] Several malignancies associated with PWS have also been reported including Wilms' tumour, lymphoma, testicular tumours, ovarian teratoma, hepatoblastoma and multiple endocrine neoplasia type I.[7] In a cohort of PWS patients from Finland a non-significant increase for testicular cancer, breast cancer and leukaemia was observed.[8] Similarly, a large US survey, involving 1852 PW patients, showed an increase in the total number of observed cancer cases (8 versus 4.8 expected in the general US population) albeit a significantly increased risk for myeloid leukaemia was noticed (3 observed cases versus 0.075 expected).[9] No convincing mechanism has been proposed for this excess of cases. One possible explanation could be that the 15q11-q13 locus –the location of the genes causing PWS- may also include a gene involved in the biology of myeloid leukemias.[9] Another explanation for the excess testicular tumours could be the increased incidence of cryptorchidism –a known risk factor for testicular cancer- among PW patients.[8] An epigenetic phenomenon called genomic imprinting plays a central role in the pathogenesis of PWS. Imprinting causes genes to be expressed in a parent-of-origin-specific manner, by way of "silencing" the genes from the other sex parent via methylation. If certain genes in the PWS region of the paternally inherited chromosome 15 (15q11.2–q13) cannot be expressed- because of deletions of paternally inherited genes, maternal uniparental disomy, or imprinting defect- then PWS develops.[7] Similarly, absence of gene expression in the same area of the

maternal chromosome 15 results in Angelman syndrome.[7] These two syndromes are considered "sister imprinted disorders" with more severe cognitive and neurological impairment in Angelman and more severe behavioral and endocrine disorders in Prader-Willi syndrome.

As DNA methylation has been involved in tumorigenesis, it can be hypothesized that the mechanisms leading to the development of PWS could also be implicated in the development of certain malignancies noticed in these patients. Our patient is the first reported case of medulloblastoma in a child with Prader-Willi syndrome. We have not been able to identify a possible link between the condition and the development of the tumour especially with such aggressive behaviour.

Medulloblastoma commonly relapses (30-40%) and does not switch subgroup at the time of recurrence. [20] The location and timing of recurrence depends on the subgroup of the original tumour.[20] More recent experimental data, suggest that medulloblastomas develop altered biology at relapse with the emergence of P53-MYC interactions, that are biomarkers of clinically aggressive disease that may be targeted therapeutically.[21] The majority of relapses occur within three to five years from diagnosis although later recurrences have also been reported.[6] Our patient originally had a standard risk MBL placing her at a lower risk of relapse. Although recurrence is associated with dismal prognosis a recent study showed that a prolonged survival can be achieved with the appropriate treatment in isolated relapse in the posterior fossa in a subset of the patients.[12]

In conclusion, relapse of medulloblastoma in children can occur at unusual sites such as the pons and clinicians should be aware of this possibility. The diagnosis and management of these patients is very challenging, and the outcome is poor due the location of the tumour and the limited therapeutic options. In the hands

of experienced neurosurgeons, biopsy of the brainstem lesions is a safe tool, used to confirm the diagnosis in equivocal cases.

Figure legends

Figure 1. Axial T2, ADC and contrast enhanced T1 weighted images (A) at presentation showing the diffusion restricted and avidly enhancing pontine lesion; (B) same levels after 5 days of high dose steroids showing rapid response reduction of lesion size, reversal of diffusion changes and almost complete resolution of the enhancement and (C) same levels 2 weeks after weaning of the steroids and recurrence of symptoms showing recurrence of diffusion restriction, enhancement and further increase of the size of the lesion.

Figure 2. Contrast enhanced T1 weighted planning scan immediately before biopsy and 7 days after of recommencement of steroid treatment, showing rapid response to steroids.

REFERENCES

1. Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. *Crit Rev Oncol Hematol.* 2016; 105:35-51.
2. Louis DN, Perry A, Reifenberger, G et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-20.
3. Waszak SM , Northcott PA, Buchhalter I et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort**.** *Lancet Oncol.* 2018; (published online May 8.)
4. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatr Blood Cancer*. 2014;61:1398-1402.
5. Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro Oncol*. 2013;15:97-103.
6. Warmuth-Metz M, Blashofer S, von Bueren AO, et al. Recurrence in childhood medulloblastoma. *J Neurooncol*. 2011;103:705-711.
7. Cassidy SB, Driscoll DJ. Prader-Willi syndrome. *Eur J Hum Genet*. 2008; 17:3-13.
8. Patja K, Sund R, Kaski M, et al. Cancer incidence among persons Prader-Willi syndrome in Finland. *Int J Disab Hum Dev*. 2008; 7:69–72.
9. Davies HD, Leusink GL, McConnell A, et al. Myeloid leukemia in Prader-Willi syndrome. J Pediatr. 2003;142(2): 174-178.

10. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol. 2012; 30(26): 3187-3193.
11. Packer RJ, Sutton LN, Elterman R, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. *J Neurosurg*. 1994; 81(5): 690-698
12. Sabel M, Fleischhack G, Tippelt S, et al. Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study. *J Neurooncol*. 2016; 129(3): 515-524.
13. Lim BC, Chae JH, Kim SK, et al. Aquaporin-4 autoimmunity masquerading as a brainstem tumor. *J Neurosurg Pediatr.* 2014;11: 1-5.
14. Trend P, Youl BD, Sanders MD, et al. Vertical gaze palsy due to a resolving midbrain lesion. *J Neurol Neurosurg Psychiatry* 1990;53:708-709.
15. Mizock BA, Bartt R, Agbemazdo B. Herpes zoster oticus with pontine lesion: segmental brain-stem encephalitis. *Clin Infect Dis.* 2000;30:229-230.
16. Kim JH, Chung PW, Oh S, et al. Ramsay Hunt syndrome complicated by a brainstem lesion. J Clin Virol. 2007;39: 322-325.
17. Lee KY, Lee YJ, Kim TH, et al. Clinico-radiological spectrum in enterovirus 71 infection involving the central nervous system in children. *J Clin Neurosci*. 2014;21:416-420.
18. Zeng H, Wen F, Gan Y, et al. MRI and associated clinical characteristics of EV71-induced brainstem encephalitis in children with hand-foot-mouth disease. *Neuroradiology* 2012; 54:623-630.
19. Weintraub L, Miller T, Friedman I, et al. Misdiagnosing recurrent

283 medulloblastoma: the danger of examination and imaging without histological
284 confirmation. *J Neurosurg Pediatr*. 2014;13: 33-37.
285 20. Ramaswamy V, Remke M, Bouffet E, et al. 2013. Recurrence patterns across
286 medulloblastoma subgroups: an integrated clinical and molecular analysis. *Lancet*
287 *Oncol*. 2013; 4: 1200–1207.
288 21. Hill RM, Kuijper S, Lindsey JC, et al. Combined MYC and P53 defects emerge
289 at medulloblastoma relapse and define rapidly progressive, therapeutically
290 targetable disease. *Cancer Cell*. 2015; 27(1):72-84.