Case Report

Pediatric Neurosurgery

Pediatr Neurosurg 2008;44:501–508
DOI: 10.1159/000187125

Received: January 28, 2008
Accepted after revision: July 28, 2008
Published online: January 6, 2009

A Novel *TP53* Germline Mutation in a Family with a History of Multiple Malignancies: Case Report and Review of the Literature

Pankaj K. Agarwalla[a] Ian F. Dunn[a] Christopher D. Turner[c] Keith L. Ligon[b]
Katherine A. Schneider[c] Edward R. Smith[a]

[a]Department of Neurosurgery and [b]Division of Neuropathology, Children's Hospital of Boston, and
[c]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Mass., USA

Key Words
Choroid plexus carcinoma · Li-Fraumeni syndrome · TP53 protein

Abstract
Objective: Choroid plexus carcinoma (CPC) has been associated with *TP53* germline mutations and Li-Fraumeni syndrome (LFS). We describe our finding of a novel germline mutation in the *TP53* gene in a family with multiple malignancies and in association with a child presenting with CPC. ***Method:*** An 8-month-old male presented with seizure-like activity; imaging disclosed a 1.5-cm left ventricular mass confirmed to be CPC intra- and postoperatively. Family history was significant for a half-sister who died of a primary CNS sarcoma and a paternal grandmother negative for *BRCA1*, *BRCA2*, *MLH1*, and *MSH2* mutations with multiple (>6) LFS spectrum malignancies. ***Results:*** Familial *TP53* testing revealed an A→T substitution at DNA position 13071, creating a deleterious Asn→Ile substitution at amino acid 131 in exon 5. ***Conclusion:*** Physicians treating patients with CPC should be attuned to reviewing family history for risk factors suggestive of genetic cancer syndromes such as LFS. These syndromes markedly influence both the patient and family members and may alter postoperative treatment regimens.

Introduction

Li-Fraumeni syndrome (LFS) was first described in 1969 and is an autosomal dominant hereditary cancer syndrome conferring high susceptibility to breast cancer, sarcomas, and childhood malignancies including brain tumors in affected individuals [1–5]. Li-Fraumeni-like (LFL) syndromes have also been described and have been defined in various ways [6, 7]. Germline mutations in the *TP53* gene are associated with the majority of families with LFS and LFL. The *TP53* tumor suppressor gene on chromosome 17p13 encodes the p53 protein which is a transcription factor important in apoptosis and cell cycle control and frequently mutated in human cancers [8–11]. Table 1 summarizes the diagnostic criteria for both LFS and LFL.

Primary choroid plexus carcinoma (CPC) in childhood has sporadically been associated with the LFSs [12–15]. We describe here a new *TP53* germline mutation arising in an LFS family with a proband who was an infant when diagnosed with a primary CPC, a half-sibling who died of primary leptomeningeal sarcomatosis as an infant, and a paternal grandmother diagnosed with multiple malignancies before 45 years of age, including breast cancer [16]. This unique family and germline mutation are described and the literature linking LFS and CPC is reviewed.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1016–2291/08/0446–0501$24.50/0

Accessible online at:
www.karger.com/pne

Edward R. Smith, MD
Department of Neurosurgery, Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115 (USA)
Tel. +1 617 355 8414, Fax +1 617 730 0906, E-Mail edward.smith@childrens.harvard.edu

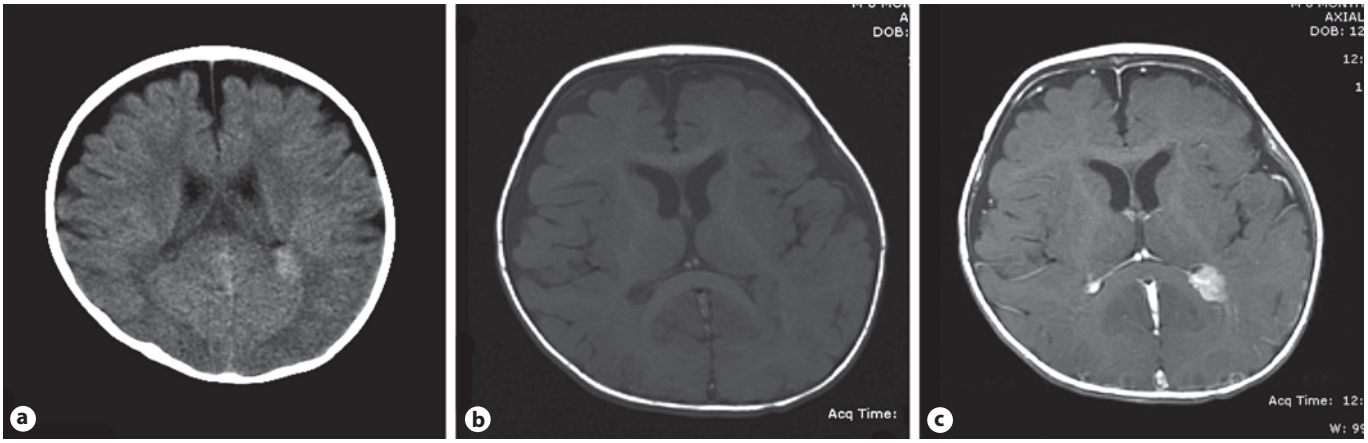


Fig. 1. Axial radiographic images of proband at time of presentation showing enhancing left ventricular mass. **a** CT. **b** T_1-weighted MRI without contrast. **c** T_1-weighted MRI with contrast.

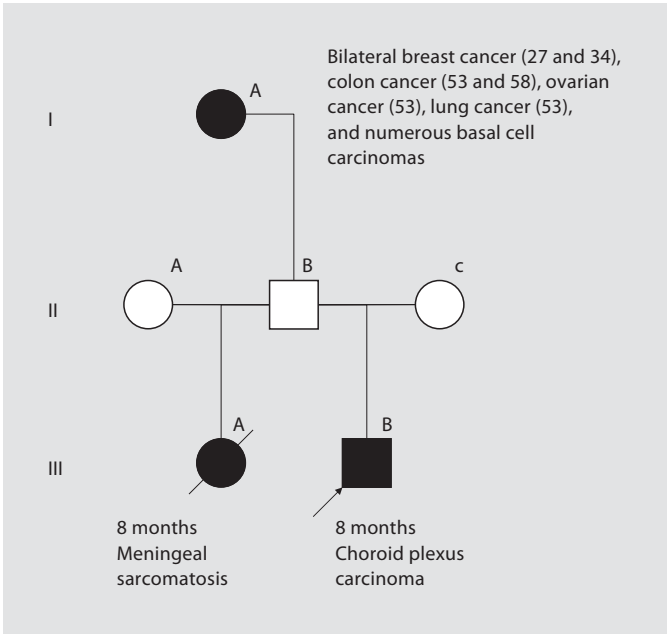


Fig. 2. Family history of patient. The numbers in parentheses refer to the age at diagnosis in years. The father of the proband is considered to be a nonpenetrant carrier who may manifest disease.

Case Report

History

An 8-month-old Caucasian male presented to his primary care pediatrician with 6 weeks of sporadic tremors of both upper extremities. At the pediatrician's office, the patient's physical and neurological exam was normal, but as the patient's half-sister had died of disseminated meningeal sarcomatosis 2 years before, the pediatrician obtained a head computed tomography scan (CT) which revealed a 1.5-cm hyperdense lesion in the atrium of the left ventricle (fig. 1a). There was mild prominence of the ventricles and the subarachnoid space overlying both frontal lobes and no evidence of midline shift or herniation. Subsequent MRI of the brain demonstrated a 1.2 × 1.6 × 1.8 cm avidly enhancing lobulated mass within the atrium extending into the occipital horn of the left lateral ventricle, lateral to the choroid plexus (fig. 1b, c). The lesion had restricted diffusion, but MR spectroscopy was not suggestive of a high-grade tumor (not shown). The cerebellar tonsils were in normal position and spinal imaging was negative.

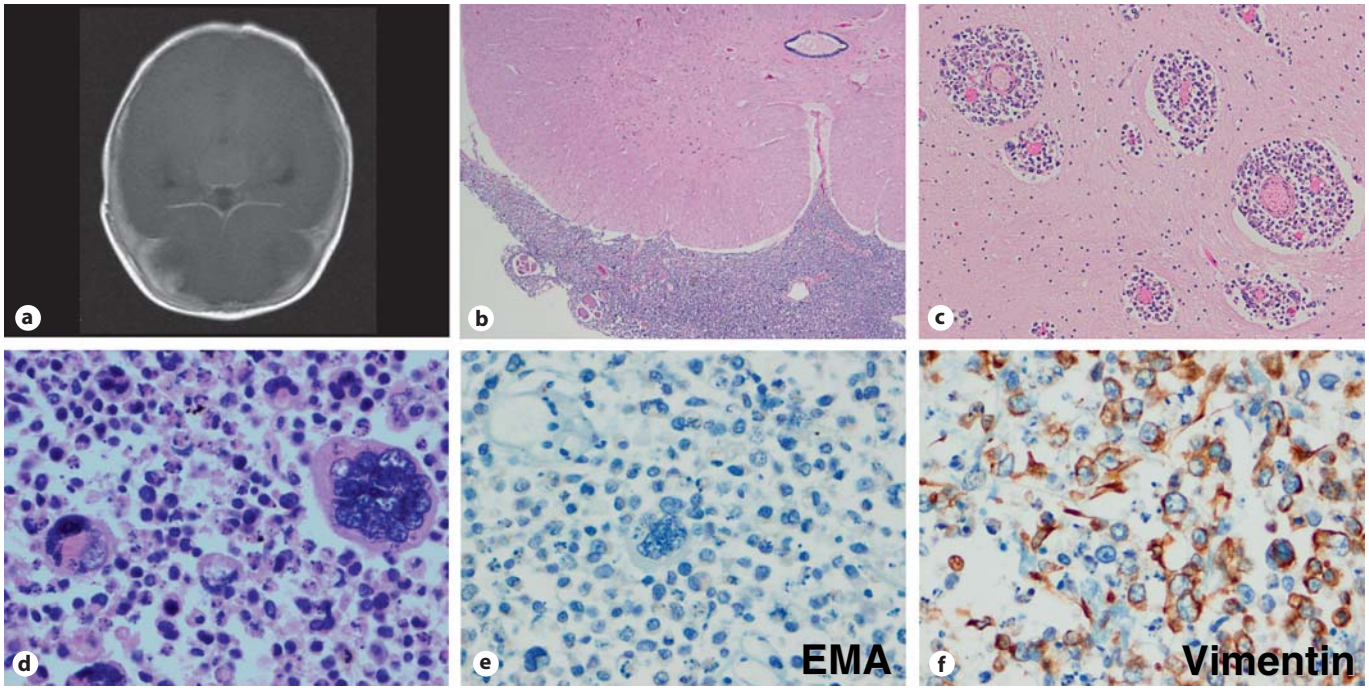
Past Medical History

The patient was the product of a full-term pregnancy complicated by maternal lupus and was delivered by a normal spontaneous vaginal delivery. He was healthy except for the sporadic tremors and met all developmental milestones. His immunizations were complete and he was on no medications at the time of diagnosis.

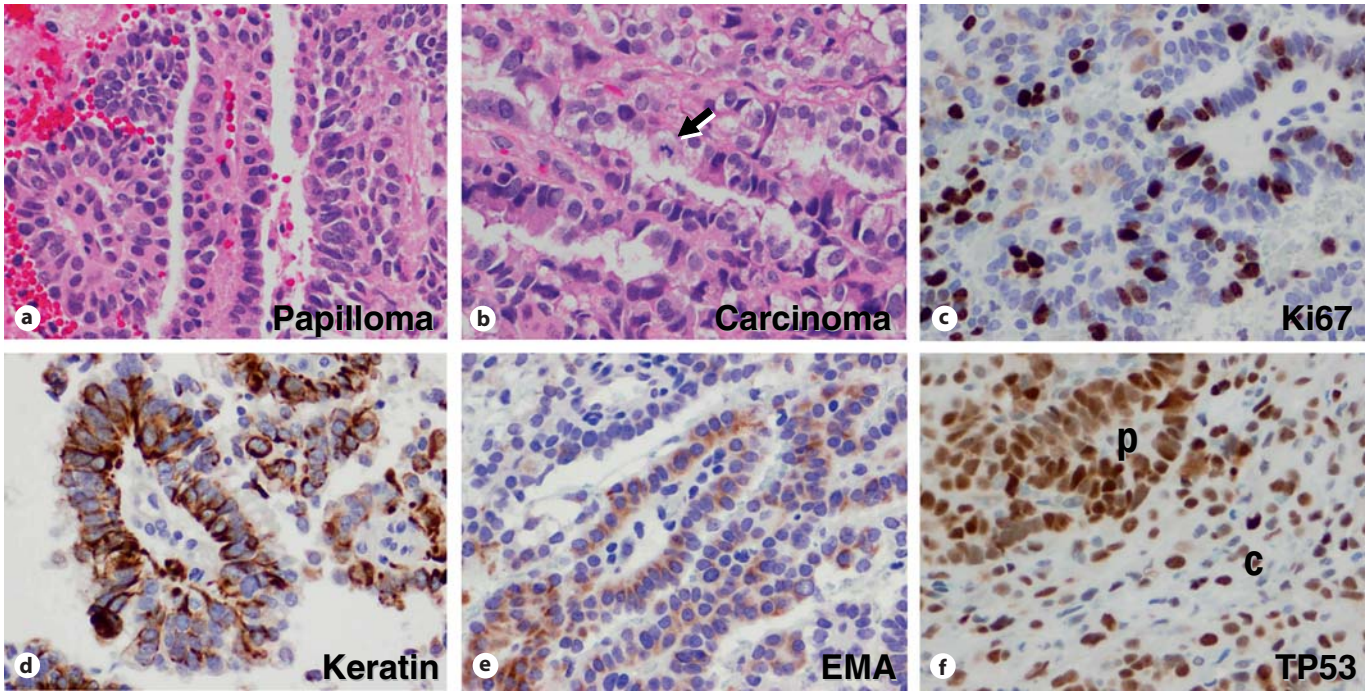
Family History

The patient's family tree is shown in figure 2. The patient's mother and father were both in their early twenties and were healthy with no known medical problems. However, the patient's father had an infant daughter from a previous relationship who died of diffuse CNS cancer. This paternal half-sister (III-A) presented 2 years previously, also at 8 months of age, with vomiting, dehydration, acute otitis media, and what was thought to be gastroenteritis. The symptoms worsened and the patient became lethargic, then acutely nonresponsive while hospitalized. MRI showed diffuse cerebral edema with abnormal leptomeningeal enhancement of the brain and spine, with no definitive mass identified (fig. 3a). The patient met brain death criteria and was taken off of life support.

An autopsy revealed extensive and diffuse involvement of the leptomeninges, posterior fossa and spinal cord by a polymorphic variant of primary leptomeningeal sarcomatosis. There was no clearly identifiable mass lesion. Microscopic examination showed diffuse involvement of the leptomeninges and Virchow-Robin



3



4

Fig. 3. a Axial contrast-enhanced MRI showing diffuse cerebral edema with abnormal leptomeningeal enhancement. **b** Low-power image with diffuse neoplastic involvement of the leptomeninges and Virchow-Robin spaces. Medium-power (**c**) and high-power (**d**) images of tumor with pleomorphism, necrosis, apoptosis and high mitotic activity. **e** Immunohistochemical staining negative for epithelial markers (EMA). **f** Immunopositivity for intermediate filament marker, vimentin.

Fig. 4. a Papilloma regions of neoplasm with preserved papillary morphology and moderate atypia, with rare mitoses. **b** Carcinoma regions of neoplasm with marked atypia, loss of papillary architecture, and a high mitotic rate (arrow shows mitotic figure). **c** MIB-1 proliferation index was 25%. **d** Positive keratin stain. **e** Positive epithelial marker antigen (EMA) staining. **f** High levels of nuclear *TP53* expression in papilloma (p) as well as carcinoma (c) regions.

spaces by a highly malignant neoplasm (fig. 3b); the tumor was discohesive and showed marked pleomorphism, necrosis, apoptosis and high mitotic activity (fig. 3c, d). Immunohistochemical staining revealed that the tumor was negative for epithelial markers (fig. 3e) but expressed the intermediate filament marker vimentin, a characteristic of mesenchymal tumors (fig. 3f). Cytogenetic analysis of the tumor showed multiple numerical and structural abnormalities in multiple chromosomes, but no clear diagnostic pattern.

The patient's paternal grandmother (I-A) was alive at the age of 58 years, but has a long history of multiple primary malignancies. She had separate primary breast cancers diagnosed at ages 27 and 34 years. She was diagnosed with colon cancer at ages 53 and 58 and ovarian and lung cancer at age 53. She also reported having over 40 basal cell carcinomas removed to date. She was previously tested and found negative for the breast cancer genes BRCA1 and BRCA2 and for the DNA mismatch repair genes MLH1 and MSH2. She was, however, found to have a balanced Robertsonian translocation, 45,t(13;14), that was thought to be unrelated. Testing for TP53 was requested, but insurance requests to fund it were denied and the testing was not performed at that time. Additional malignancies in the family include a paternal great-grandmother with chronic lympocytic leukemia at the age of 48 and colorectal cancer at the age of 62.

Operation

Following the MRI diagnosis of a mass, the patient underwent a left parieto-occiptial craniotomy to establish a tissue diagnosis and decompress the ventricular system. Intraoperative ultrasound enabled a minimal corticectomy; the edge of the left ventricle was opened longitudinally and the tumor presented as grayish, friable, and hemorrhagic. It was well encapsulated, did not appear to adhere to the surrounding brain, and arose from a pedicle of choroid which was gently freed. It was felt that a gross total resection was achieved as the entire tumor was removed and the ventricle was inspected for any remaining tumor, with none found.

Pathology

The neoplasm was composed of a variable mixture of regions corresponding to CPC with small regions of choroid plexus papilloma (fig. 4a, b). Papilloma regions exhibited preserved papillary morphology and moderate atypia, with rare mitoses (fig. 4a). Carcinoma regions had marked atypia, loss of papillary architecture and a high mitotic rate (fig. 4b). The MIB-1 proliferation index was 25% (fig. 4c) and the tumor exhibited characteristic staining for epithelial markers (keratin and EMA; fig. 4d, e). The tumor had high levels of nuclear TP53 expression in papilloma as well as carcinoma regions (fig. 4f).

Postoperative Course and Adjuvant Treatment

The postoperative MRI was negative for residual tumor, but for definitive therapy the patient was enrolled in a Pediatric Brain Tumor Consortium Clinical Trial consisting of systemic and intrathecal (IT) chemotherapy for infants with embryonal tumors. An Ommaya catheter was placed for IT delivery of mafosfamide and a Port-A-Cath was placed for venous access. The patient began 20 weeks of chemotherapy consisting of intravenous administration of cyclophosphamide, vincristine, cisplatin, followed by 21 days of oral etoposide. Mafosfamide was administered IT twice weekly concurrent with the systemic chemotherapy. However, the IT chemotherapy was discontinued after 4 doses due to an adverse reaction.

After 20 weeks of treatment, a surveillance MRI revealed the patient had developed a trapped left lateral horn; the patient underwent a left pterional craniotomy for fenestration of left temporal horn with microdissection and biopsy of tumor bed. There was no recurrent tumor visible during the secondary operation, and all biopsy specimens were negative for tumor.

At this point in the patient's treatment, the patient's paternal grandmother had been confirmed to have a new *TP53* mutation and due to the increased risk of secondary malignancy in this genetic background the decision was made to forgo any additional chemotherapy or radiation therapy. Thus, all tumor-directed therapy was completed and the patient entered a period of close observation. Two months after fenestration, routine CT and MR imaging showed an increasing dilatation of the left temporal horn and re-entrapment, for which the patient had ventriculoperitoneal shunt placed. The patient is currently doing well.

Genetic Testing

During the patient's treatment, the family was referred for genetic counseling. The patient's paternal grandmother was tested for *TP53* mutation given the concern for *TP53*-related hereditary cancer syndrome, and she was found to harbor a new germline *TP53* mutation.

The mutation is a single basepair substitution, A→T, at DNA position 13071, resulting in a deleterious Asn→Ile substitution at amino acid 131 in a conserved region of exon 5, a component of the DNA-binding domain [11]. Given the evidence of a familial cancer syndrome, the patient's father was later tested and was found to have the identical germline *TP53* mutation. The patient himself was not tested for two significant reasons: (1) The family would have endured significant cost to themselves for further genetic testing of the patient as their insurance company refused testing given the clear evidence of a hereditary *TP53* mutation, and (2) there remains significant ethical discussion on genetic testing of minors when they are not capable of making an informed decision of whether they wish to be tested themselves.

Discussion

While astrocytomas (40–55%), medulloblastomas (20–30%), and ependymomas (10–15%) account for the majority of CNS tumors in children under the age of 15, choroid plexus tumors (CPTs) represent 1–5% of CNS tumors in this population according to several large series, with an even higher incidence in patients under the age of 2 [16–21]. About 20% of these are CPCs which are more malignant than choroid plexus papillomas [16, 19, 22]. Interestingly, the location of CPTs in pediatric patients primarily tends to be supratentorial – particularly the left atrium – while the adult population has infratentorial CPTs [16]. The survival in the pediatric population with CPTs is higher for papillomas than carcinomas [18, 19].

Despite the rarity of CPCs, there is growing evidence for the association of these carcinomas with familial cancer syndromes, particularly LFS. Li and Fraumeni defined their eponymous syndrome based on a specific autosomal dominantly inherited pattern, including specific cancers [2, 4, 5, 23]. The Li-Fraumeni 'narrow spectrum' of cancers includes soft-tissue sarcomas, osteosarcomas, CNS tumors, adrenocortical tumors, and premenopausal breast cancers [9, 24, 25]. Birch et al. [1] broadened the original definition by codifying the LFL. The diagnostic criteria for both LFS and LFL are given in table 1. Because of our patient's dominant inheritance pattern, our patient's family fits the LFS criteria: with the patient's half-sister defined as the proband with a sarcoma, our patient is a first-degree relative with a CNS tumor, and the grandmother is a second-degree relative with cancer before the age of 45. It is important to note that the association of primary leptomeningeal sarcomatosis with *TP53* mutation and hereditary syndromes has not been well described, although LFS patients frequently develop sarcomas at a young age. In 1990, both Malkin et al. [3] and Srivastava et al. [26] found associations between germline *TP53* mutations and families with LFS. Numerous studies have found a similar association, although germline *TP53* mutations are only found in approximately 70% of classic LFS cases with an even lower incidence in LFL or families with a history of primary LFS spectrum tumors [1, 7, 10, 27–31].

The *TP53* tumor suppressor gene on chromosome 17p13 encodes a 53-kDa, 393-amino-acid phosphoprotein (hence p53) which is a transcription factor important in apoptosis and cell cycle control [8–11]. The p53 protein has four major functional domains: transactivation (1–50), DNA binding (102–292), tetramerization (323–356), and negative regulation (363–393) [11, 32]. Furthermore, cross-species sequence analysis has revealed five major regions of conservation within the following amino acid residues: 13–23, 117–142, 171–181, 234–250, and 270–286. Pathological consequences of p53 mutation include loss of normal p53 function, dominant-negative mutations that can alter wild-type p53 function, and even a rare form of translocation defect with cytoplasmic accumulation and nuclear exclusion, seen particularly in certain regulatory domain mutations [32]. The proband's N311I missense mutation falls within a conserved region in the DNA-binding domain and led to a loss of function of tumor suppressor activity [11]. Based on a functional analysis with 8 different promoters, the N131I mutation was found to have less than 20% transactivational activity and is a nonfunctional mutant [33, 34]. Having consulted three major p53 databases, we report this N131I germline mutation as a novel germline *TP*53 mutation and add to previous reports of N131I as a somatic mutation [34–42].

Table 1. Diagnostic criteria for LFS and LFL

LFS criteria [2]
1 Proband with a sarcoma before age 45
2 Plus a 1st-degree relative with cancer in this age interval
3 Plus a close (1st- or 2nd-degree) relative in the lineage with either a sarcoma at any age or any cancer before age 45
LFL criteria [1]
1 A proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed under 45 years
2 Plus a 1st- or 2nd-degree relative with a typical LFS cancer diagnosed at any age (sarcoma, breast cancer, brain tumor, leukemia, or adrenocortical carcinoma)
3 Plus a 1st- or 2nd-degree relative in the same lineage with any cancer diagnosed before age 60

It has been shown that certain mutant forms of p53 can have significantly increased half-lives and/or increased concentration when compared to wild-type p53 [43, 44]. Furthermore, an immunohistochemical analysis of the N131I mutation in a sample of urinary bladder carcinoma revealed increased staining of p53 [39]. Taken together, it is not surprising to find increased staining of p53 in our pathological specimen.

Garber et al. [14] first made the association of CPCs with LFS in 3 cases, 1 index case and 2 updated cases previously described in 1988 [2]. Since their 3 cases, there have been 17 additional cases, including this report, of primary CPC, occurring in patients with LFS/LFL, germline *TP53* mutations, or both [12, 13, 15, 29, 45–50]. The number of such cases may be underestimated since many reports do not distinguish between types of CNS tumors or divide CPTs into papillomas and carcinomas [1–5, 23, 25, 26, 51, 52]. In addition, a case of a primary CPC occurring in a patient without any family history of cancer who most likely had a de novo germline *TP53* mutation has been reported [53]. CPCs have also been reported in association with other cancer syndromes. Sévenet et al. [54, 55] suggest an association of CPCs with rhabdoid predisposition syndrome, characterized by mutations in *hSNF5/INI* and by carcinomas that have a strong phenotypic correlation to those with *TP53* mutations.

While Ohgaki et al. [56] describe four CPCs without any *TP53* mutation, it is nevertheless important to recognize that primary CPC in the pediatric patient, especial-

ly at an early age, has been associated with an underlying hereditary disposition to cancer. Therefore, because of the association of such tumors with familial cancer syndromes, it is imperative for the treating physician who sees a CPC to record a complete family history and consider the presence of a familial cancer syndrome.

Optimal postoperative treatment for infants and children with CPC remains controversial. At the time our patient presented, most recent evidence suggested that survival was improved by radical surgical resection followed by adjuvant treatment [19]. Nevertheless, since there was no known optimal treatment, standard of care was to enroll the patient in an open clinical trial as appropriate. Instead of not pursuing further adjuvant treatment, the family chose to enroll in our clinical trial to evaluate the postoperative use of IT chemotherapy followed by radiation for intracranial embryonal CNS tumors. Since then, there has been growing evidence that there is a survival benefit to chemotherapy, particularly in cases of subtotal resection [12, 57–60].

Therefore, management goals in treating such a tumor, especially in the case of LFS/LFL, should include total resection with appropriate postoperative chemotherapy [18, 19, 61]. Patients should be started immediately on corticosteroid therapy after the diagnosis and en bloc resection should be attempted after gaining control of vascular supply intraoperatively [16]. In the case of any patient with a hereditary disposition for cancer, but especially with germline *TP53* mutations, it is imperative to avoid radiotherapy due to the substantial risk of radiation-induced secondary malignancies [62] in light of the central role of p53 in the DNA damage response after radiation. Furthermore, the benefits of adjuvant or postoperative chemotherapy must be weighed against the risks, given reports of increased rates of secondary malignancies such as myelodysplastic syndrome and leukemias [45, 63]. With total surgical resection and chemotherapy, survival rates for CPCs are most likely slightly higher than the 50% recorded by Ellenbogen et al. [18].

Conclusion

We describe the case of a young child with CPC whose family meet the criteria for LFS. We add to both the genetic and the neurosurgical literature by reporting a novel *TP53* germline mutation in this family, and in reviewing the literature emphasize that CPC in children should prompt the acquisition of a careful family history.

Acknowledgements

The authors would like to thank Drs. Christopher Pierson and Umberto DeGirolami for sharing their pathological findings on leptomeningeal sarcomatosis.

References

1 Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, Harris M, Jones PH, Binchy A, Crowther D, et al: Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994;54:1298–1304.

2 Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW: A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358–5362.

3 Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, et al: Germline p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–1238.

4 Li FP, Fraumeni JF Jr: Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969;71:747–752.

5 Li FP, Fraumeni JF Jr: Rhabdomyosarcoma in children: epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 1969;43:1365–1373.

6 Eeles RA: Germline mutations in the tp53 gene. Cancer Surv 1995;25:101–124.

7 Birch JM, Heighway J, Teare MD, Kelsey AM, Hartley AL, Tricker KJ, Crowther D, Lane DP, Santibanez-Koref MF: Linkage studies in a Li-Fraumeni family with increased expression of p53 protein but no germline mutation in p53. Br J Cancer 1994;70:1176–1181.

8 Malkin D: The role of p53 in human cancer. J Neurooncol 2001;51:231–243.

9 Frebourg T, Abel A, Bonaiti-Pellie C, Brugieres L, Berthet P, Bressac-de Paillerets B, Chevrier A, Chompret A, Cohen-Haguenauer O, Delattre O, Feingold J, Feunteun J, Frappaz D, Fricker JP, Gesta P, Jonveaux P, Kalifa C, Lasset C, Leheup B, Limacher JM, Longy M, Nogues C, Oppenheim D, Sommelet D, Soubrier F, Stoll C, Stoppa-Lyonnet D, Tristant H: Le syndrome de Li-Fraumeni: mise au point, données nouvelles et recommandations pour la prise en charge. Bull Cancer 2001;88:581–587.

10 Melean G, Sestini R, Ammannati F, Papi L: Genetic insights into familial tumors of the nervous system. Am J Med Genet C Semin Med Genet 2004;129:74–84.

11 Soussi T, Beroud C: Assessing tp53 status in human tumours to evaluate clinical outcome. Nat Rev Cancer 2001;1:233–240.

12 Dickens DS, Dothage JA, Heideman RL, Ballard ET, Jubinsky PT: Successful treatment of an unresectable choroid plexus carcinoma in a patient with Li-Fraumeni syndrome. J Pediatr Hematol Oncol 2005;27:46–49.

13 Krutilkova V, Trkova M, Fleitz J, Gregor V, Novotna K, Krepelova A, Sumerauer D, Kodet R, Siruckova S, Plevova P, Bendova S, Hedvicakova P, Foreman NK, Sedlacek Z: Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline tp53 mutations. Eur J Cancer 2005;41:1597–1603.

14 Garber JE, Burke EM, Lavally BL, Billett AL, Sallan SE, Scott RM, Kupsky W, Li FP: Choroid plexus tumors in the breast cancer-sarcoma syndrome. Cancer 1990;66:2658–2660.

15 Yuasa H, Tokito S, Tokunaga M: Primary carcinoma of the choroid plexus in Li-Fraumeni syndrome: case report. Neurosurgery 1993;32:131–133; discussion 133–134.
16 Ellenbogen RG, Scott RM: Choroid plexus tumors; in Kaye AH, Laws ER (eds): Brain Tumors: An Encyclopedic Approach. London, Churchill Livingstone, 2001, pp 551–562.
17 Pascual-Castroviejo I, Villarejo F, Perez-Higueras A, Morales C, Pascual-Pascual SI: Childhood choroid plexus neoplasms. A study of 14 cases less than 2 years old. Eur J Pediatr 1983;140:51–56.
18 Ellenbogen RG, Winston KR, Kupsky WJ: Tumors of the choroid plexus in children. Neurosurgery 1989;25:327–335.
19 Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM: Choroid plexus tumours. Br J Cancer 2002;87:1086–1091.
20 Rickert CH, Paulus W: Epidemiology of central nervous system tumors in childhood and adolescence based on the new who classification. Childs Nerv Syst 2001;17:503–511.
21 Stiller CA, Bleyer WA: Epidemiology; in Walker DA (ed): Brain and Spinal Tumors of Childhood. London, Arnold, 2004, pp 35–49.
22 Laurence KM: The biology of choroid plexus papilloma in infancy and childhood. Acta Neurochir (Wien) 1979;50:79–90.
23 Li FP, Fraumeni JF Jr: Prospective study of a family cancer syndrome. JAMA 1982;247:2692–2694.
24 Nichols KE, Malkin D, Garber JE, Fraumeni JF Jr, Li FP: Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 2001;10:83–87.
25 Birch JM, Alston RD, McNally RJ, Evans DG, Kelsey AM, Harris M, Eden OB, Varley JM: Relative frequency and morphology of cancers in carriers of germline tp53 mutations. Oncogene 2001;20:4621–4628.
26 Srivastava S, Zou ZQ, Pirollo K, Blattner W, Chang EH: Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature 1990;348:747–749.
27 Varley JM: Germline tp53 mutations and Li-Fraumeni syndrome. Hum Mutat 2003;21:313–320.
28 Frebourg T, Barbier N, Yan YX, Garber JE, Dreyfus M, Fraumeni J Jr, Li FP, Friend SH: Germ-line p53 mutations in 15 families with Li-Fraumeni syndrome. Am J Hum Genet 1995;56:608–615.
29 Chompret A, Brugieres L, Ronsin M, Gardes M, Dessarps-Freichey F, Abel A, Hua D, Ligot L, Dondon MG, Bressac-de Paillerets B, Frebourg T, Lemerle J, Bonaiti-Pellie C, Feunteun J: P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer 2000;82:1932–1937.
30 Evans DG, Birch JM, Thorneycroft M, McGown G, Lalloo F, Varley JM: Low rate of tp53 germline mutations in breast cancer/sarcoma families not fulfilling classical criteria for Li-Fraumeni syndrome. J Med Genet 2002;39:941–944.
31 Eng C, Schneider K, Fraumeni JF Jr, Li FP: Third international workshop on collaborative interdisciplinary studies of p53 and other predisposing genes in Li-Fraumeni syndrome. Cancer Epidemiol Biomarkers Prev 1997;6:379–383.
32 May P, May E: Twenty years of p53 research: structural and functional aspects of the p53 protein. Oncogene 1999;18:7621–7636.
33 Kato S, Han SY, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C: Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci USA 2003;100:8424–8429.
34 Olivier M, Eeles R, Hollstein M, Khan MA, Harris CC, Hainaut P: The IARC TP53 database: new online mutation analysis and recommendations to users. Hum Mutat 2002;19:607–614.
35 Hamroun D, Kato S, Ishioka C, Claustres M, Beroud C, Soussi T: The UMD TP53 database and website: update and revisions. Hum Mutat 2006;27:14–20.
36 Sedlacek Z, Kodet R, Poustka A, Goetz P: A database of germline p53 mutations in cancer-prone families. Nucleic Acids Res 1998;26:214–215.
37 Le Calvez F, Mukeria A, Hunt JD, Kelm O, Hung RJ, Taniere P, Brennan P, Boffetta P, Zaridze DG, Hainaut P: Tp53 and kras mutation load and types in lung cancers in relation to tobacco smoke: distinct patterns in never, former, and current smokers. Cancer Res 2005;65:5076–5083.
38 Tannapfel A, Busse C, Weinans L, Benicke M, Katalinic A, Geissler F, Hauss J, Wittekind C: Ink4a-arf alterations and p53 mutations in hepatocellular carcinomas. Oncogene 2001;20:7104–7109.
39 Bernardini S, Adessi GL, Billerey C, Chezy E, Carbillet JP, Bittard H: Immunohistochemical detection of p53 protein overexpression versus gene sequencing in urinary bladder carcinomas. J Urol 1999;162:1496–1501.
40 Hsieh LL, Hsia CF, Wang LY, Chen CJ, Ho YS: P53 gene mutations in brain tumors in Taiwan. Cancer Lett 1994;78:25–32.
41 Williamson MP, Elder PA, Knowles MA: The spectrum of tp53 mutations in bladder carcinoma. Genes Chromosomes Cancer 1994;9:108–118.
42 Lee HJ, Kim JS, Ha SJ, Roh KY, Seo EJ, Park WS, Lee JY, Park KS, Kim JW: P53 gene mutations in Bowen's disease in Koreans: clustering in exon 5 and multiple mutations. Cancer Lett 2000;158:27–33.
43 Olson DC, Levine AJ: The properties of p53 proteins selected for the loss of suppression of transformation. Cell Growth Differ 1994;5:61–71.
44 Vogelstein B, Kinzler KW: P53 function and dysfunction. Cell 1992;70:523–526.
45 Broniscer A, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE: Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. Cancer 2004;100:2246–2252.
46 Jolly KW, Malkin D, Douglass EC, Brown TF, Sinclair AE, Look AT: Splice-site mutation of the p53 gene in a family with hereditary breast-ovarian cancer. Oncogene 1994;9:97–102.
47 Malkin D, Chilton-MacNeill S, Meister LA, Sexsmith E, Diller L, Garcea RL: Tissue-specific expression of sv40 in tumors associated with the Li-Fraumeni syndrome. Oncogene 2001;20:4441–4449.
48 Sedlacek Z, Kodet R, Seemanova E, Vodvarka P, Wilgenbus P, Mares J, Poustka A, Goetz P: Two Li-Fraumeni syndrome families with novel germline p53 mutations: loss of the wild-type p53 allele in only 50% of tumours. Br J Cancer 1998;77:1034–1039.
49 Vital A, Bringuier PP, Huang H, San Galli F, Rivel J, Ansoborlo S, Cazauran JM, Taillandier L, Kleihues P, Ohgaki H: Astrocytomas and choroid plexus tumors in two families with identical p53 germline mutations. J Neuropathol Exp Neurol 1998;57:1061–1069.
50 Wyatt-Ashmead J, Kleinschmidt-DeMasters B, Mierau GW, Malkin D, Orsini E, McGavran L, Foreman NK: Choroid plexus carcinomas and rhabdoid tumors: phenotypic and genotypic overlap. Pediatr Dev Pathol 2001;4:545–549.
51 Quesnel S, Verselis S, Portwine C, Garber J, White M, Feunteun J, Malkin D, Li FP: P53 compound heterozygosity in a severely affected child with Li-Fraumeni syndrome. Oncogene 1999;18:3970–3978.
52 Frebourg T: Germline mutations of the p53 gene. Pathol Biol (Paris) 1997;45:845–851.
53 Wang L, Cornford ME: Coincident choroid plexus carcinoma and adrenocortical carcinoma with elevated p53 expression: a case report of an 18-month-old boy with no family history of cancer. Arch Pathol Lab Med 2002;126:70–72.
54 Sévenet N, Lellouch-Tubiana A, Schofield D, Hoang-Xuan K, Gessler M, Birnbaum D, Jeanpierre C, Jouvet A, Delattre O: Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype correlations. Hum Mol Genet 1999;8:2359–2368.
55 Sévenet N, Sheridan E, Amram D, Schneider P, Handgretinger R, Delattre O: Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. Am J Hum Genet 1999;65:1342–1348.

56 Ohgaki H, Eibl RH, Schwab M, Reichel MB, Mariani L, Gehring M, Petersen I, Holl T, Wiestler OD, Kleihues P: Mutations of the p53 tumor suppressor gene in neoplasms of the human nervous system. Mol Carcinog 1993;8:74–80.
57 Fiorillo A, Maggi G, Cirillo S, Migliorati R, Buffardi F, Alfieri E, Sabbatino MS, D'Amico A, DelBasso DeCaro ML: Efficacy of sequential chemotherapy including methotrexate and doxorubicin in an infant with partially resected choroid plexus carcinoma. Pediatr Neurosurg 2003;38:21–26.
58 Fitzpatrick LK, Aronson LJ, Cohen KJ: Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected? J Neurooncol 2002;57:123–126.
59 Greenberg ML: Chemotherapy of choroid plexus carcinoma. Childs Nerv Syst 1999;15:571–577.
60 Wrede B, Liu P, Wolff JE: Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors. J Neurooncol 2007;85:345–351.
61 Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, Kalifa C, Brunelle F, Sgouros S, Meyer P, Cinalli G, Zerah M, Pierre-Kahn A, Renier D: Papillomas and carcinomas of the choroid plexus in children. J Neurosurg 1998;88:521–528.
62 Evans DG, Birch JM, Ramsden RT, Sharif S, Baser ME: Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet 2006;43:289–294.
63 Duffner PK, Krischer JP, Horowitz ME, Cohen ME, Burger PC, Friedman HS, Kun LE: Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: a Pediatric Oncology Group study. Ann Neurol 1998;44:313–316.