J Neurooncol (2010) 96:437–441
DOI 10.1007/s11060-009-9978-1

CASE REPORT

Low-grade astrocytoma in a child with encephalocraniocutaneous lipomatosis

María Sol Brassesco · Elvis Terci Valera · Aline Paixão Becker · Angel Mauricio Castro-Gamero · André de Aboim Machado · Antônio Carlos Santos · Carlos Alberto Scrideli · Ricardo Santos Oliveira · Hélio Rubens Machado · Luiz Gonzaga Tone

Received: 15 May 2009 / Accepted: 13 July 2009 / Published online: 4 August 2009

Abstract Encephalocutaneous lipomatosis (ECCL), or Haberland syndrome, is an uncommon congenital disorder with unique cutaneous, ocular and neurological features. In the present article, we describe a 3-year-old boy with ECCL who developed an extensive and recurring intraventricular low-grade glioma with atypical pathological features and elevated mitotic index. Cytogenetic analysis from tumor sample was also performed. This is the first report of a low-grade astrocytoma occurring in a child with ECCL. Whether or not the origin of the tumor is associated to the pathogenesis of the underlying syndrome is a matter for further investigation.

Keywords Astrocytoma · Brain tumor · Childhood cancer · ECCL · Genetic disorder

Introduction

Encephalocraniocutaneous lipomatosis (ECCL) is a rare congenital neurocutaneous disease first described by Haberland and Perou in 1970 [1]. The disorder affects primarily tissues and organs of ectodermal and mesodermal origin unilaterally even though bilateral involvement has seldom been reported [2, 3]. The cutaneous lesions include lipomas (associated with overlying alopecia), angiofibromas, hyperostosis, and connective tissue nevi usually located in the scalp and periocular area. Ipsilateral cerebral malformations are also common and, as a consequence, most patients have mental retardation, seizures, and behavioral problems, without a confirmed relationship with the site and the extent of the anatomic damage [4].

To date, only approximately 50 patients have been reported (reviewed in [5]). In the present article, we present the case of a 3-year-old boy with ECCL who developed an extensive and recurring intraventricular low-grade glioma.

Case report

A 2-month-old male was referred to our institution by a general pediatrician who observed an area of alopecia in the scalp and failure to thrive. He was the first child from a healthy non-consanguineous couple. The pregnancy was

María Sol Brassesco and Elvis Terci Valera have contributed equally.

M. S. Brassesco · E. T. Valera · C. A. Scrideli · L. G. Tone
Division of Pediatric Oncology, Department of Pediatrics, University of São Paulo, São Paulo, Brazil

A. P. Becker
Department of Pathology, University of São Paulo, São Paulo, Brazil

A. M. Castro-Gamero
Department of Genetics, University of São Paulo, São Paulo, Brazil

A. de Aboim Machado · A. C. Santos
Radiology Division, University of São Paulo, São Paulo, Brazil

R. S. Oliveira · H. R. Machado
Division of Neurosurgery, Department of Surgery and Anatomy, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil

M. S. Brassesco (✉)
Laboratório de Pediatria – Bloco G. Av. Bandeirantes, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – USP, 3900. Bairro Monte Alegre, CEP 14048-900 Ribeirão Preto, SP, Brazil
e-mail: marsol@rge.fmrp.usp.br; solbrassesco@hotmail.com

complicated by a miscarriage warning in the third month of gestation. On physical examination, there was an extensive area of *alopecia areata* over the occipital region. In addition, colobomas in the left eye (eyelid and iris) were observed. The child was karyotypically normal, 46, XY. The diagnosis of ECCL was suspected and an encephalic magnetic resonance imaging (MRI) revealed a mass in the posterior fossa with contiguous extension to the scalp that was compatible with an encephalocraniocutaneous lipoma (Fig. 1a, b). The child was submitted to a partial surgical resection of the lesion, and the diagnosis of lipoma was confirmed by histopathological exam. He was followed at the outpatient clinics with an uneventful evolution (Fig. 1c).

At the age of three years, he developed sudden strabismus, vomiting, headaches, and seizures. A new MRI showed an expanding lesion located at the suprasellar region and extending throughout the hypothalamus and third ventricles (Fig. 1d–g). The patient was submitted to a left fronto-parietal craniotomy with a near-total resection of the lesion. Three months later, he presented with signs of intracranial hypertension. The MRI revealed a short-term recurrence of the disease. He was resubmitted to surgical procedure with subtotal resection (Fig. 1h). No adjuvant treatment was offered. Subsequent MRIs showed a stable residual tumor (Fig. 1i). The child remains in short-term (6 months) remission, under close clinical and radiological surveillance.

Microscopic examination of the specimen showed a neuroepithelial neoplasm, composed of round and elongated (piloid) cells, with focal pleomorphim. Rosenthal fibers and eosinophilic granular bodies were scarce. The cells were arranged in a fibrillary background. Mitotic figures were rare and necrosis was absent, but there were multiple areas of microvascular proliferation. Immunohistochemically (IH), tumor cells were positive for glial fibrillary acid protein (clone GFAP, 1:6,000; Dako®) and galectin-3 (clone 9C4, 1:200; Novocastra®). Negative reaction included Neu-N (clone Isotype IgG, 1:2,000; Chemicon International®). Proliferative index measured by Ki67 antigen (clone MIB-1, 1:300; Dako®) was 15% in the most mitotically active area (Fig. 2). Based upon morphological and IH findings, the diagnostic was of a pilocytic astrocitoma, grade I in the World Health Organizations (WHO) classification, with focal atypia and high proliferative index.

Cytogenetic preparations from fresh tumor sample (adjacent to areas verified by frozen section), were obtained

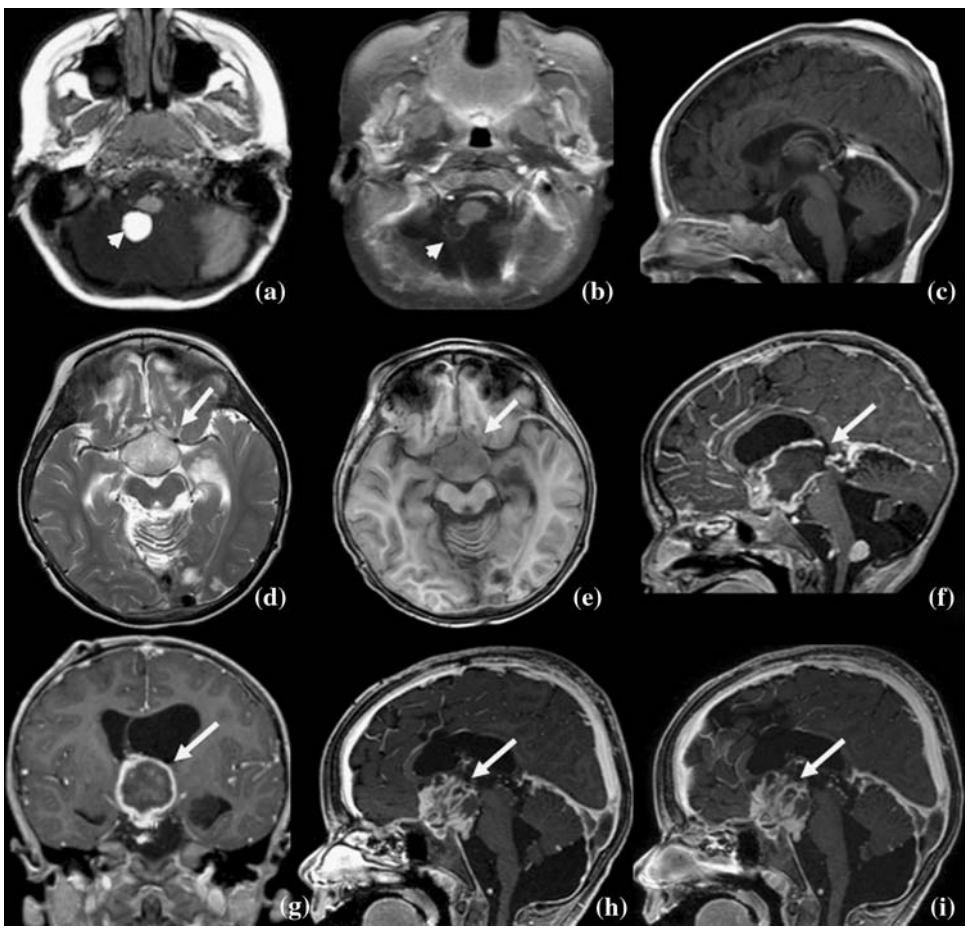

Fig. 1 Magnetic resonance imaging acquired with a 1.5T equipment (Magneton Vision, Siemens, Erlanger, Germany) showing two time points of the patient evolution. **a–c** The first exam at 2 years of age shows lipoma (*arrow head*) confirmed by the fat suppression sequence (**b**), and no lesion in the suprasellar topography is observed in sagittal T1-weighted post-gadolinium sequences (**c**). **d–g** The second MRI at 3 years of age shows the suprasellar tumor (*arrow*). **d** T2-weighted axial TSE sequence **f** T1-weighted pre-gadolinium axial sequence **e–g** Sagital and coronal T1-weighted post-gadolinium sequences. Note the heterogeneous lesion with peripheral enhancement at the hypothalamus histological proved pilocytic astrocytoma. **h**, **i** Images in sagital T1-weighted post-gadolinium sequences after surgical procedure with subtotal resection (**h**) and 3 months after this exam with stable residual tumor (**i**)

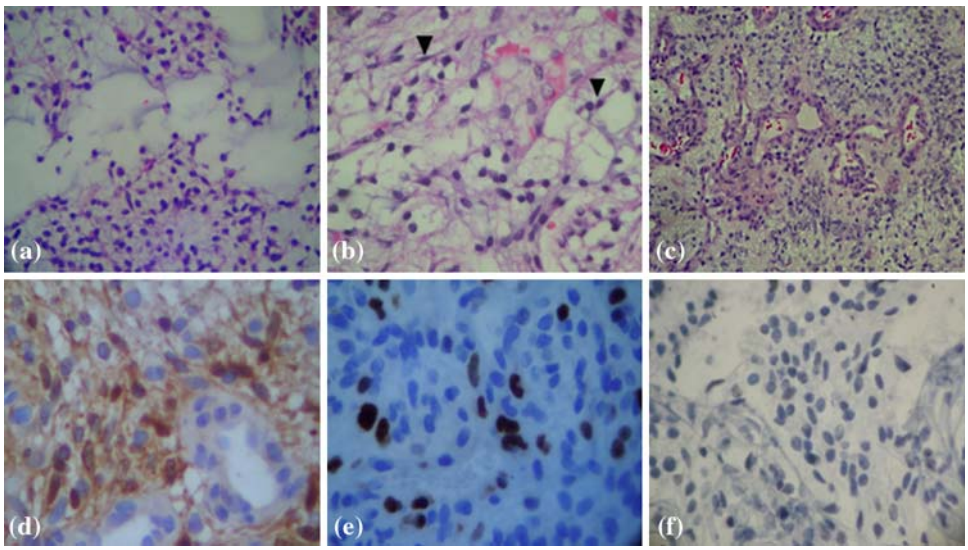

Fig. 2 Histopathological aspect from the lesion. **a** Biphasic neoplasm, with microcystic areas (H&E, ×100); **b** round cells and piloid cells (*arrowheads*) disposed in fibrillar background (H&E, ×200); **c** microvascular proliferation (H&E, ×100); **d** galectin-3 reaction, with nuclear and citoplasmatic positivity, and negative reaction in the endothelium (×400); **e** nuclear positivity for Ki67 (×400); **f** p53 immunorreaction resulted negative

as previously described in Brassesco et al. [6], and GTG-banding results were interpreted according to the International System for Human Cytogenetic Nomenclature 2005 guidelines [7]. Tumor cultured cells showed a normal karyotype 46,XY. Cytogenetic analysis of the sample by CGH also showed normal hybridization patterns without any evidence of gain or loss of genetic material Fig. 3.

This study was approved by the Research Ethics Committee of the Clinical Hospital of the Faculty of Medicine of Ribeirão Preto—USP (*Proc: 6591/2007*).

Discussion

ECCL etiology is uncertain. All cases described in the literature have been sporadic without any geographic, racial, or sex predilection. No patterns of inheritance have been described and no chromosomal aberration has been demonstrated [8]. It has been suggested that the origin of this disorder could be a lethal autosomal mutation that survives in mosaicism [9, 10], or be caused by environmental damage that affects embryonic development of ectomesodermal tissues [8]. Among the 50 cases described in the literature, only one case of a child with this syndrome and features of neurofibromatosis type 1 (NF-1) has been reported [11], although it is possible that both ECCL and NFI occurred coincidentally in that patient.

In the present study, we report the case of a 3-year-old boy with ECCL who developed an extensive and recurring intraventricular pilocytic glioma. Karyotype analysis of tumor culture by GTG-banding showed a normal chromosome complement which was confirmed by CGH.

Despite the progress made towards improving survival for children with brain tumors, little is known about the molecular genetic events that contribute to tumor initiation or progression. Consistent tumor-specific chromosomal

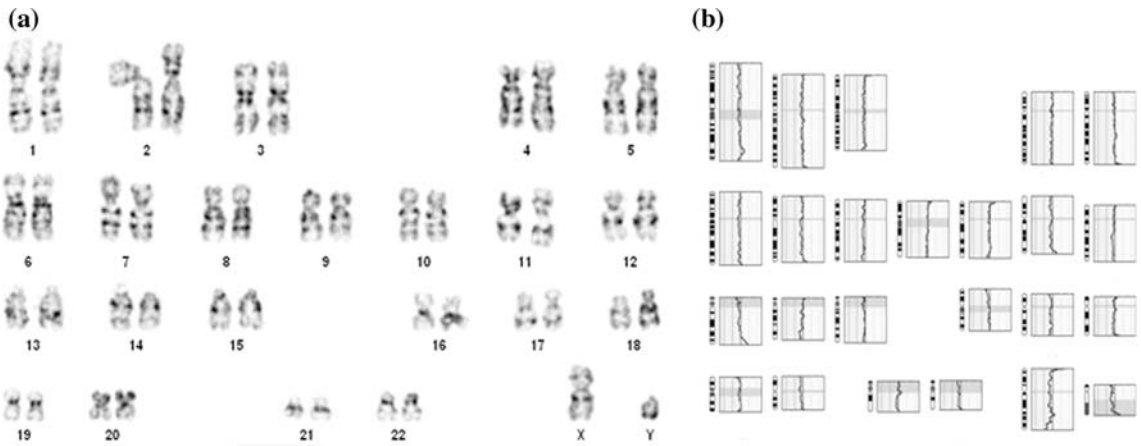

Fig. 3 **a** Conventional cytogenetic analysis of Giemsa-Trypsin-banded childhood pilocytic astrocytoma showing normal karyotype 46,XY; **b** CGH analysis showing normal hybridization patterns

aberrations have not been demonstrated in childhood low-grade astrocytic tumors. Mutations of the *TP53* tumor suppressor gene [12] and loss of heterozygosity on the short arm of chromosome 17 have been frequently described in adult patients [13]. Also, gains of 7q [14] mainly 7q34 with increased BRAF-MEK-ERK signaling have been described as common findings in this cohort [15]. However, cytogenetic analyses of pediatric pilocytic astrocytomas have shown mostly normal karyotypes [16]. In sporadic cases, minimal simple chromosomes changes involving chromosomes 7, 8, and 11 [17, 18] and telomeric associations [19, 20] have been described. Also, genome analyses by array-CGH have shown whole chromosomal gains (with more participation of chromosomes 5 and 7) in pediatric cases with an increasing tendency along with age [21]. Nonetheless, as seen in the majority of low-grade central nervous system tumors, normal chromosome complements are often the frequent finding, pointing to the possibility of small copy number changes, or deregulated epigenetic modifications.

Approximately 10% of children with brain tumors have a genetic disorder that places them at increased risk for developing cancer [22]. Some well-described associations occur between neurofibromatosis (with *NF-1* gene mutation) and low-grade or optic nerve gliomas [23], Turcot syndrome (with *APC* gene mutation), and Gorlin syndrome (with germline mutation of the Sonic Hedgehog receptor *PTCH*) with medulloblastoma [24]. Moreover, tuberous sclerosis, with involvement of *TSC1* and *TSC2* genes, is highly associated to subependymal giant-cell astrocytomas (SEGA) [25]. Most of these syndromes display an autosomal dominant pattern of inheritance and some of them, particularly NF, are highly incident in the general population, making the association "genetic disorder and propensity to cancer" easier to demonstrate by statistical models.

Similar to the majority of neurocutaneous syndromes, ECCL seems to show a propensity to develop tumors, which are generally non-progressive benign lipomas. However, few tumors other than lipomas have been reported in association with ECCL syndrome, which include ossifying fibromas [2], odontomas [26], and osteomas [27, 28]. Interestingly, no CNS tumor has been previously reported in association with ECCL syndrome.

This is the first report of a low-grade astrocytoma occurring in a child with ECCL. Whether this intriguing and rare syndrome displays a genetic background that could ultimately predispose to the development of low-grade gliomas in children deserves further investigation.

Acknowledgement This research was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP Proc. No: 07/54236-4, 06/04827-3 and 07/04065-9).

References

1. Haberland C, Perou M (1970) Encephalocraniocutaneous lipomatosis. A new example of ectomesodermal dysgenesis. Arch Neurol 22:144–155
2. MacLaren MJ, Kluijt I, Koole FD (1995) Ophthalmologic abnormalities in encephalocraniocutaneous lipomatosis. Doc Ophthalmol 90:87–98
3. Rubegni P, Risulo M, Sbano P, Buonocore G, Perrone S, Fimiani M (2003) Encephalocraniocutaneous lipomatosis (Haberland syndrome) with bilateral cutaneous and visceral involvement. Clin Exp Dermatol 28(4):387–390
4. Fishman MA, Chang CSC, Miller JA (1978) Encephalocraniocutaneous lipomatosis. Pediatrics 61:580–582
5. Moog U, Jones MC, Viskochil DH, Verloes A, Van Allen MI, Dobyns WB (2007) Brain anomalies in encephalocraniocutaneous lipomatosis. Am J Med Genet 143A(24):2963–2972
6. Brassesco MS, Valera ET, Neder L, Castro-Gamero AM, Arruda D, Machado HR, Sakamoto-Hojo ET, Tone LG (2008) Polyploidy in atypical grade II choroid plexus papilloma of the posterior fossa. Neuropathology 29(3):293–298. doi:10.1111/j.1440-1789.2008.00949.x
7. Shaffer LG, Tommerup N (2005) ISCN 2005: an international system for human cytogenetic nomenclature. Karger, Basel
8. Gawel J, Schwartz RA, Józwiak S (2003) Encephalocraniocutaneous lipomatosis. J Cutan Med Surg 7(1):61–65
9. Happle R, Steijlen PM (1993) A non-hereditary mosaic phenotype Encephalocraniocutaneous lipomatosis. Hautarzt 44(1):19–22
10. Hamm H (1999) Cutaneous mosaicism of lethal mutations. Am J Med Genet 85(4):342–345
11. Legius E, Wu R, Eyssen M et al (1995) Encephalocraniocutaneous lipomatosis with a mutation in the NF1 gene. J Med Genet 32:316–319
12. Rasheed BK, McLendon RE, Herndon JE, Friedman HS, Friedman AH, Bigner DD, Bigner SH (1994) Alterations of the TP53 gene in human gliomas. Cancer Res 54(5):1324–1330
13. Bigner SH, McLendon RE, Fuchs H, McKeever PE, Friedman HS (1997) Chromosomal characteristics of childhood brain tumors. Cancer Genet Cytogenet 97(2):125–134
14. Schröck E, Blume C, Meffert MC, du Manoir S, Bersch W, Kiessling M, Lozanowa T, Thiel G, Witkowski R, Ried T, Cremer T (1996) Recurrent gain of chromosome arm 7q in low-grade astrocytic tumors studied by comparative genomic hybridization. Genes Chromosomes Cancer 15(4):199–205
15. Bar EE, Lin A, Tihan T, Burger PC, Eberhart CG (2008) Frequent gains at chromosome 7q34 involving BRAF in pilocytic astrocytoma. J Neuropathol Exp Neurol 67(9):878–887
16. Griffin CA, Long PP, Carson BS, Brem H (1992) Chromosome abnormalities in low-grade central nervous system tumors. Cancer Genet Cytogenet 60(1):67–73
17. Zattara-Cannoni H, Gambarelli D, Lena G, Dufour H, Choux M, Grisoli F, Vagner-Capodano AM (1998) Are juvenile pilocytic astrocytomas benign tumors? A cytogenetic study in 24 case. Cancer Genet Cytogenet 104(2):157–160
18. Orr LC, Fleitz J, McGavran L, Wyatt-Ashmead J, Handler M, Foreman NK (2002) Cytogenetics in pediatric low-grade astrocytomas. Med Pediatr Oncol 38(3):173–177
19. Harrison KJ, Neumann E, Kalousek DK, Norman MG, Masui S, Harrison K (1994) Astrocytoma with a unique telomere association. Cancer Genet Cytogenet 76(1):33–35
20. Roberts P, Chumas PD, Picton S, Bridges L, Livingstone JH, Sheridan E (2001) A review of the cytogenetics of 58 pediatric brain tumors. Cancer Genet Cytogenet 131(1):1–12

21. Jones DT, Ichimura K, Liu L, Pearson DM, Plant K, Collins VP (2006) Genomic analysis of pilocytic astrocytomas at 0 97 Mb resolution shows an increasing tendency toward chromosomal copy number change with age. J Neuropathol Exp Neurol 65(11): 1049–1058
22. Blaney SM, Kun LE, Hunter J, Rorke-Adams LB, Lau C, Strother D, Pollack IF (2006) Tumors of the central nervous system. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. Lippincott Williams & Wilkins, Philadelphia, pp 786–864
23. Gutmann DH (2008) Using neurofibromatosis-1 to better understand and treat pediatric low-grade glioma. J Child Neurol (10): 1186–1194
24. Lo Muzio L (2008) Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis 3:32
25. Napolioni V, Moavero R, Curatolo P (2009) Recent advances in neurobiology of tuberous sclerosis complex. Brain Dev 31(2): 104–113
26. Andreadis DA, Rizos CB, Belazi M, Peneva M, Antoniades DZ (2004) Encephalocraniocutaneous lipomatosis accompanied by maxillary compound odontoma and juvenile angiofibroma: report of a case. Birth Defects Res A Clin Mol Teratol 70(11):889–891
27. Zielińska-Kaźmierska B, Grodecka J, Jabłońska-Polakowska L, Arkuszewski P (2005) Mandibular osteoma in the encephalocraniocutaneous lipomatosis. Craniomaxillofac Surg 33(4):286–289
28. Moog U, Roelens F, Mortier GR, Sijstermans H, Kelly M, Cox GF, Robson CD, Kimonis VE (2007) Encephalocraniocutaneous lipomatosis accompanied by the formation of bone cysts: harboring clues to pathogenesis? Am J Med Genet A 143A(24): 2973–2980