Clin Neuroradiol (2019) 29:581–586
https://doi.org/10.1007/s00062-019-00820-1

CLINICAL CASE

Freiburg Neuropathology Case Conference

Hypersalivatory Seizures in a 6-year-old Child

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Published online: 6 August 2019

Keywords Hypersalivatory seizures · Ganglioglioma · Dysembryoplastic neuroepithelial tumors · Pilocytic astrocytoma · Multinodular and vacuolating neuronal tumor · Angiocentric glioma

Case Report

A 6-year-old girl had suffered from refractory epilepsy with hypersalivatory seizures for 2 years. She showed no neurological deficits and development was normal. Non-invasive evaluation with magnetic resonance imaging (MRI) revealed a lesion in the left insular cortex. The seizures persisted under medication with oxcarbazepine, levetiracetam and brivaracetam, also associated with side effects, such as fatigue and emotional instability. The electroencephalogram (EEG) showed an epileptogenic focus left centroparietal. As decided in the interdisciplinary epilepsy case conference, an extended lesionectomy was performed. The operation was navigation-guided via transsylvian preparation. The lesion was glassy, partly cystic and typically tumor-like. The tumor could be removed completely. The postoperative course was uneventful and the patient remained seizure-free (Engel class Ia) until now.

Imaging

The T2 images showed a cortical thickening accompanied with cystic changes at the level of the left insular cortex (Fig. 1, arrowhead). On fluid-attenuated inversion recovery (FLAIR) images the lesion appeared hyperintense (Fig. 2, arrowhead) whereas on T1-weighted inversion recovery images the signal of the lesion was slightly increased when compared to the cerebral cortex (Fig. 3, arrow head). On T1-weighted non-contrast images the tumour displayed a ring-like hyperintensity when compared to the surrounding cortex (Fig. 4a, arrowhead). On T1-weighted images after i.v. administration of gadolinium the lesion revealed marked circular contrast enhancement (Fig. 4b, arrowhead).

Differential Diagnosis

Ganglioglioma

Gangliogliomas are uncommon tumors of the central nervous system (CNS) predominantly seen in children and young patients presenting with temporal lobe epilepsy, as these tumors are the most common neoplastic cause of chronic temporal lobe epilepsy [1, 2]. Although gangliogliomas may occur in any part of the brain parenchyma, they are commonly located in the temporal lobe [1, 2]. Gangliogliomas are mostly well-differentiated neuroepithelial tumors with various proportions of both neural ganglionic cells and neoplastic glial cell components. Gangliogliomas are classified as World Health Organization (WHO) grade I neoplasms; however, due to the potential presence of aggressive histopathological features and malignant transformation, predominantly of the glial components, a minority of these tumors show aggressive behavior and are then graded as anaplastic ganglioglioma (WHO grade III) [3, 4]. Furthermore, fibrovascular stroma and focal calcification are common histopathological findings as well as proof of glial fibrillary acid protein (GFAP) and neuronal markers such as synaptophysin and chromogranin

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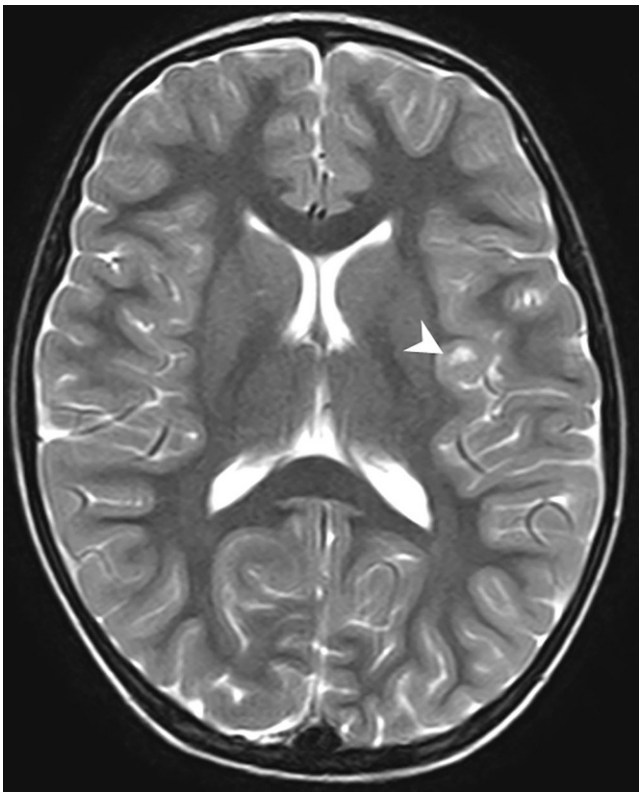

Fig. 1 Axial T2 images show a cortical thickening accompanied with cystic changes at the level of the left insular cortex (*arrowhead*)

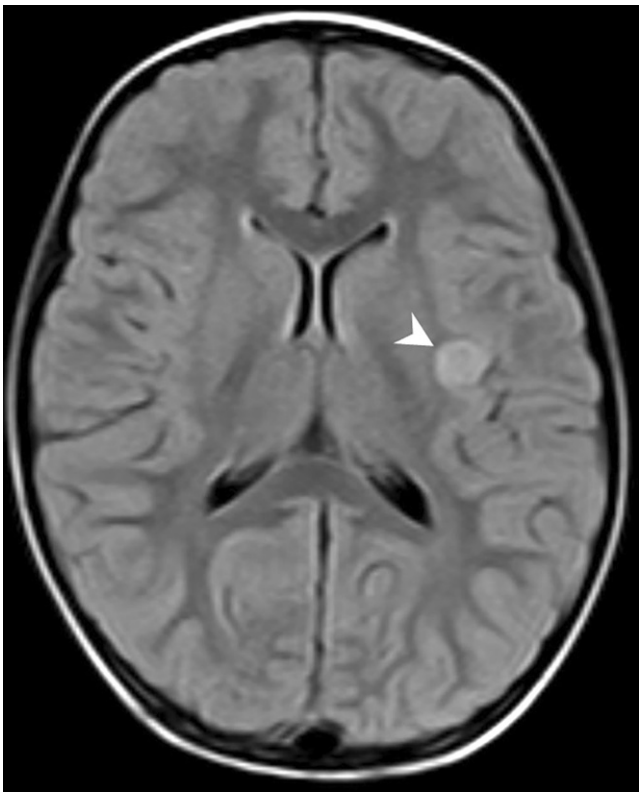

Fig. 2 On axial FLAIR images the lesion appears hyperintense (*arrowhead*)

A [5]. Usually, a positive immunoreactivity for CD34 can be detected [5]. Beside dysembryoplastic neuroepithelial tumors (DNET) and pilocytic astrocytoma, gangliogliomas often have BRAF mutations [1, 3]. Imaging findings of ganglioglioma are often non-specific, presenting with variable features: lesions are often well-circumscribed, partially cystic and located in the cortex, whereas peritumoral edema is rare. In MRI, solid components of ganglioglioma are often reported as isointense to hypointense to gray matter on T1-weighted sequences and hyperintense on T2-weighted sequences [1, 6]. Calcifications as well as mural nodules can be frequently detected and solid tumor components are enhanced in approximately half of the cases [1].

Dysembryoplastic Neuroepithelial Tumors

First described in 1988 DNET are slowly growing, glioneuronal entities, usually seen in children and young adults with intractable epilepsy (WHO grade I) [3, 7]. The DNETs are typically centered in cortical grey matter, often occurring supratentorially in the temporal or frontal lobe. In up to 80%, DNETs are associated with cortical dysplasia [7]. In imaging, DNET often occur as well-shaped multicystic intracortical masses "pointing" toward the ventricle with an expansion of the involved gyrus [7, 8]. Due to a slow growth rate, surrounding edema and the perifocal mass effect are minimal to absent [7, 8]. In MRI, lesions appear hyperintense on T2 and hypointense in T1-weighted sequences with a characteristic bright rim in FLAIR sequences [7, 8]. Usually, calcification is rare in DNET lesions and heterogeneous enhancement patterns have been reported [7, 8].

Due to the described imaging features and missing association with cortical dysplasia, the diagnosis of a DNET in the presented is case is less likely.

Pilocytic Astrocytoma

Pilocytic astrocytomas are low-grade well-defined astrocytomas, classified as WHO grade I neoplasms [3]. Accounting for approximately 17% of all pediatric brain tumors, the pilocytic astrocytoma is the most common primary brain tumor in children with a peak incidence between 5 and 15 years old [9]. Furthermore, a strong association with neurofibromatosis type 1 exists, as 15% of the patients develop pilocytic astrocytoma. Pilocytic astrocytomas predominantly arise from midline structures and are commonly located in the cerebellum, involving the cerebellar hemisphere and vermis, followed by the optic pathway, especially in patients with neurofibromatosis type 1 [9, 10]. Clinically, headache, visual loss due to affected optic path-

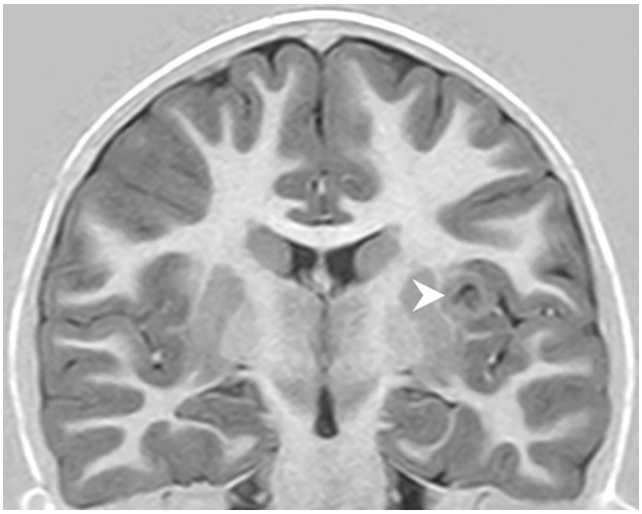

Fig. 3 On coronal T1-weighted inversion recovery images the signal intensity of the lesion is slightly increased when compared to the cerebral cortex (*arrowhead*)

way and ataxia are common symptoms. Pilocytic astrocytoma often presents as well-circumscribed, cystic mass lesions with hyperintensity of cyst contents on T2-weighted and FLAIR sequences [10]. Typically, an intense enhancing mural nodule and ring-like enhancement of cystic components can be detected [10]. In the context of the described imaging features and localization, a diagnosis of a pilocytic astrocytoma in the present case is improbable; however, due to the fact that pilocytic astrocytoma are the most common primary pediatric brain tumor, its differential diagnosis has to be considered.

Multinodular and Vacuolating Neuronal Tumor

Until now only few cases of multinodular and vacuolating neuronal tumors (MVNT) have been reported, mostly occurring in young to middle-aged patients [11]. Initially, it remained unclear whether MVNTs were true neoplastic processes or malformed dysplastic lesions; however, according to the revised WHO classification of CNS tumors, these tumors have been recognized as low-grade mixed glial neuronal lesions since 2016 [3, 11, 12]. If asymptomatic, these lesions can be managed as "leave me alone lesions" with surveillance imaging to ensure stability [12]. In MRI, T2 hyperintense "bubbly" lesions located on the subcortical ribbon and superficial subcortical white matter following the contours of gyri in distinct U-shaped configuration are characteristic imaging findings for MVNT in MRI [11]. On T1-weighted sequences, MVNT lesions appear hypointense to isointense to the cortex, typically without enhancement or perifocal edema and without diffusion restriction on diffusion-weighted MRI [11]. Immunostaining is positive for synaptophysin but negative for GFAP [12].

Due to the missing "bubbly" pattern or U-shaped configuration along the inner surface of cortex, a diagnosis of a MVNT in the present case is less likely.

Angiocentric Glioma

Angiocentric gliomas, also known as angiocentric neuroepithelial tumor, are very rare neuroepithelial tumors with low proliferation rates, which are classified as WHO grade I neoplasms [3, 13, 14]. Angiocentric gliomas typically affect children and young adults and are strongly epileptogenic, as >95% of the patients present with intractable seizures

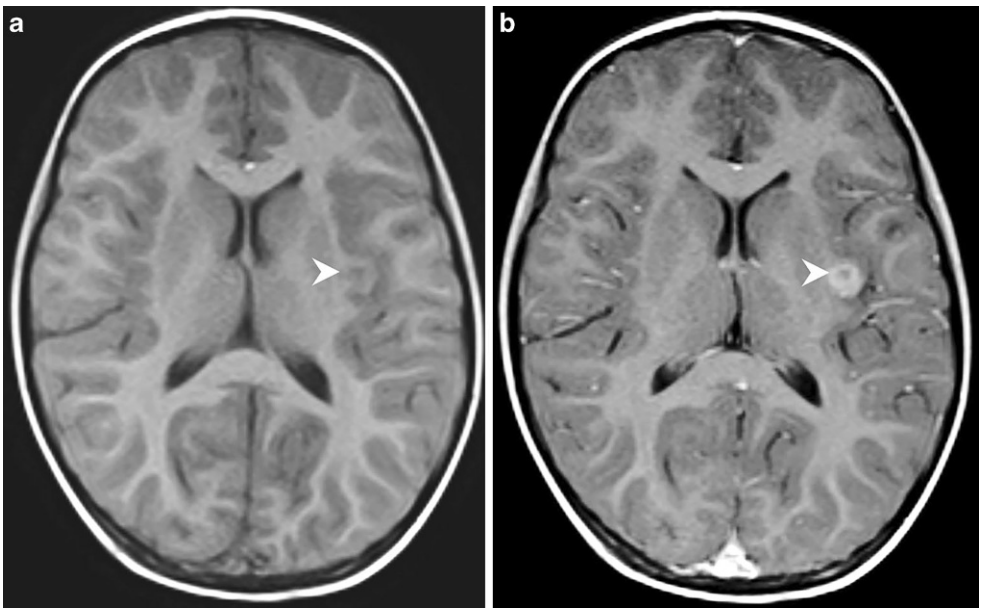

Fig. 4 On axial T1-weighted non-contrast images (**a**) the tumor displays a ring-like hyperintensity when compared to the surrounding cortex (*arrowhead*). On T1-weighted images after i.v. administration of gadolinium (**b**) the lesion reveals marked circular contrast enhancement (*arrowhead*)

[13, 14]. Typically located in the frontal lobe, angiocentric gliomas are mainly ill-defined cortically based, with stalk-like extensions into the white matter towards the ventricle [13–16]. On MRI, angiocentric glioma lesions are typically non-enhancing and hypointense on T1-weighted sequences with T1 hyperintense rims, and hyperintense on T2-weighted sequences [13–16]; however, T1 signals can be variable with weak or irregular internal enhancement after the administration of contrast agent [6, 17]. Histologically, angiocentric gliomas are characterized by bipolar glial tumor cells and a perivascular oriented growth pattern [13, 18].

The diagnosis of angiocentric glioma is consistent with the age and clinical presentation of the patient. In this case, the lesion was cortically based and demonstrated moderate ring-like hyperintensity on T1 as typical feature of angiocentric glioma; however, postcontrast enhancement of the lesion in this case is rather unusual for angiocentric gliomas.

Histology

The department of neuropathology received a biopsy sample from a pediatric patient with therapy refractory epilepsy. Histologically, the specimen appeared as a relatively isomorphic glial tumor of intermediate cell density (Fig. 5a). The tumor cell nuclei were oval-shaped with intermediate chromatin density with a characteristic "salt and pepper" structure. No mitotic figures were found in 10 randomly selected high-power fields. Nucleus-free perivascular zones were found throughout the tumor (Fig. 5a).

Immunohistochemical staining revealed glial fibrillary astrocytic protein (GFAP) positivity that was strongest

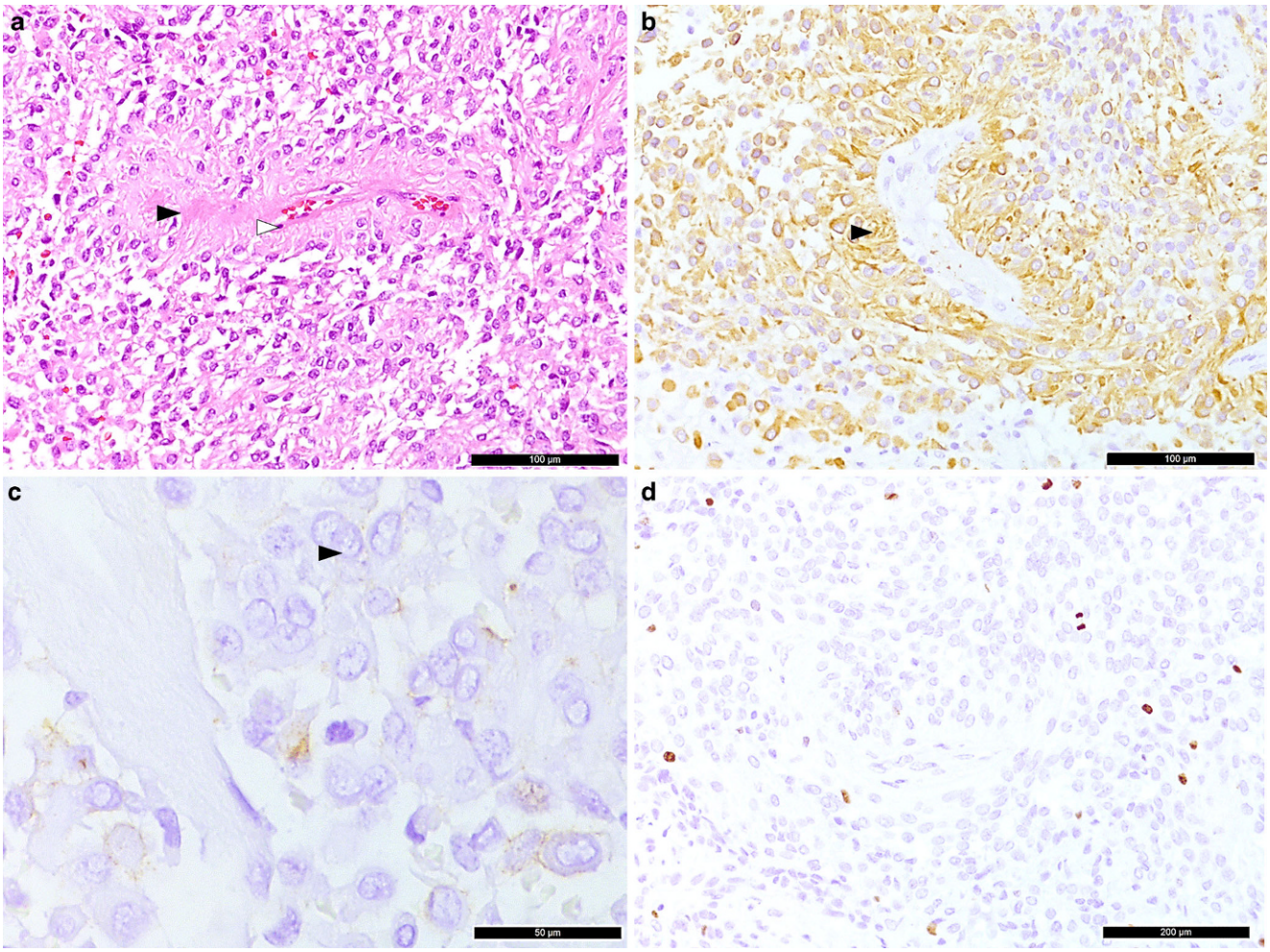

Fig. 5 Histological and immunohistochemical analyses of the tumor. Hematoxylin and eosin staining (**a**) showing the cell morphology and a characteristic nucleus-free perivascular zone (*filled arrowhead*). Note the hyalinized wall of the blood vessel (*empty arrowhead*). GFAP immunohistochemistry (**b**) was pronounced in the nucleus-free zones. The *filled arrowhead* highlights a tumor cell with a characteristic bipolar morphology and radial orientation with respect to the blood vessel. EMA positive cytosolic structures were found throughout the tumor (**c**). A Ki-67 index of 2–3% was found in the present tumor (**d**)

within perivascular nucleus-free zones (Fig. 5b). Epithelial membrane antigen (EMA) antibodies sporadically labeled cytoplasmic structures (Fig. 5c). Approximately 2–3% of the tumor cells were Ki67-positive (Fig. 5d). Immunohistochemical analyses of CD34, neurofilament, synaptophysin and the R132H mutation of isocitrate dehydrogenase I were negative. The described histological marker constellation is characteristic for an angiocentric glioma, WHO grade I. The main differential diagnosis is an ependymoma, WHO-grade II; however, due to a lack of ependymal attachment, this diagnosis was considered unlikely. Furthermore, the initially suggested differential diagnoses of glioneuronal tumors were unlikely due to CD34 negativity and the absence of interspersed neuronal structures. Molecular pathological examination using multiplex ligation-dependent probe amplification yielded negative results for deletions or amplifications of Myb, BRAF, KIAA1549, MYBL1, FGFR1 and the BRAF V600E mutation. These results in conjunction with the lack of typical histological features, made the diagnosis of a pilocytic astrocytoma, WHO grade I unlikely.

Diagnosis

Angiocentric Glioma (WHO Grade I)

Angiocentric gliomas are epilepsy-associated pediatric low-grade gliomas that display an angiocentric growth pattern with bipolar tumor cells and features associated with ependymal differentiation [19]. This entity was first defined in 2005 [13, 20]. Due to a morphological similarity to ependymomas, these tumors have previously been referred to as cortical ependymomas [21]; however, a recent genome-wide methylation profiling analysis showed a clear distinction between ependymomas and angiocentric gliomas [22]. According to an emerging molecular pathological classification of low-grade glioma, angiocentric gliomas are considered a subset of MAP kinase activated gliomas with aberrations of MYB family genes [23, 24]. In this context, MYB-QKI fusions were recently identified as the most common cause of angiocentric gliomas while IDH1, 2 and BRAF mutations have not been found [25]. Due to a low number of reported cases no data regarding incidence are available so far. Microscopically, neuronal structures may occasionally be found within the tumor, but do not display dysmorphic features [13, 20]. The mitotic activity is usually low; however, a case with multiple mitoses and poor prognosis has been described [20]. Angiocentric gliomas reported so far had overall a positive prognosis. Remission can be achieved after total resection; however, a fatal recurrence after subtotal resection has been reported [25]. Robust predictive biomarkers remain to be identified [19].

Compliance with ethical guidelines

Conflict of interest C.A. Taschner, R. Sankowski, C. Scheiwe, H. Urbach, C. Storz and M. Prinz declare that they have no competing interests.

Ethical standards All investigations described in this manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current revised form). Informed consent was obtained from the patient in this case if identifiable from images or other information within the manuscript. In the case of the underage patient in this report, informed consent was obtained from the legal representatives.

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