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Multinodular and vacuolating neuronal tumour of the cerebrum: a rare neuroimaging incidentaloma or a potentially treatable cause of focal epilepsy?

Vladimir Baščarević [1,a], Aleksa T. Pejović [2,a], Aleksandar J. Ristić [2], Nikola Vojvodić [2], Savo Raičević [1], Tijana Đukić [2], Leposava Brajković [3], Dragoslav Sokić [2]

[1] Institute for Neurosurgery,
[2] Clinic of Neurology,
[3] Institute for nuclear medicine, Clinical Center of Serbia, Medical School, University of Belgrade, Belgrade, Serbia
[a] Authors contributed equally

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ABSTRACT – Multinodular and vacuolating neuronal tumour (MVNT) of the cerebrum is a relatively new, well defined histopathological and neuroradiological entity, in many cases associated with an early adult-onset epilepsy. These lesions have an indolent course and resemble both malformative and neoplastic processes, combining a focal developmental anomaly and a low-grade tumour. Herein, we report a case of a 48-year-old female patient with left temporal lobe epilepsy associated with MVNT. In addition, a comprehensive review of all the previously published cases is provided with a focus on seizure-related cases, surgical treatment, and postoperative outcome.

Key words: multinodular vacuolating neuronal tumour, cerebrum, seizure, epilepsy, surgery, WHO tumour classification, DNET

Correspondence:
Aleksandar J. Ristić
Clinic of Neurology,
Clinical Center of Serbia,
Medical School, University of Belgrade,
Dr Subotića 6,
Belgrade, Serbia
<aristic@eunet.rs>

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The World Health Organization recently included multinodular and vacuolating neuronal tumour (MVNT) of the cerebrum in the new classification of brain tumours, recognizing its histopathological specificity (Louis *et al*., 2016). Although the first case in the literature was described by Ratilal *et al*. in 2007 (Ratilal *et al*., 2007), it was Huse and associates in 2013 who described 10 cases of a purely neuronal tumour affecting adults, in the majority of subjects (but now known to include all) presenting with seizures as their principal clinical manifestation. They characterized these lesions as an entire new benign seizure-associated entity (Huse *et al*., 2013).

Some authors speculated that MVNT is rather a dysplastic hamartomatous malformation of cortical development than a low-grade neoplasma (Cathcart *et al*., 2017; Thom *et al*., 2018). However, recent findings by Pekmezci *et al*. (2018) suggest that MVNT is a clonal neoplasm characterized by solitary pathogenic alterations that cause activation in signal transduction pathways (Ras-Raf-MAP kinase signalling pathway), and as such, this tumour is genetically similar to gangliogliomas (MVTN was present with gangliogliomas in 25% of their series), pilocytic astrocytomas, and dysembrioplastic-neuroepithelial tumours (DNET), although without the respective typical mutations.

Although rare, this novel entity is both neuropathologically and neuroradiologically well defined. Herein, we report a case of a 48-year-old female patient with left temporal lobe epilepsy associated with MVNT. In addition, a comprehensive review of all the previously published cases is provided with a focus on seizure-related cases.

Case study

The patient's index seizure (behaviour arrest and impaired awareness followed by prolonged postictal confusion) occurred at the age of 47.

At the time of the assessment, the patient was having two to three daytime seizures per month in spite of the combined therapy of valproate (2,000 mg/d) and pregabalin (300 mg/d). Previous introduction of levetiracetam failed due to the occurrence of a rash. Concomitant use of olanzapine, sertraline, and lorazepam, due to an episode of bipolar psychosis, was noted. There were no signs of any associated neurological impairment. The family history was unremarkable, and there was no history of status epilepticus.

During long-term (96-hour) video-EEG monitoring, three focal impaired awareness seizures while awake were recorded (no aura → right hand ictal dystonia/left hand automatisms → oroalimentary automatisms → postictal aphasia). Ictal EEG defined ictal onset in the left temporal region. Two independent interictal epileptiform abnormalities (in the left and right temporal region) were recorded.

Brain MRI (temporal epilepsy protocol) revealed a lesion in the left parahippocampal gyrus, extending to the hippocampus and amygdala, consisting of a cluster of variably-sized nodules, hyperintense on T2-weighted (W) and FLAIR, and slightly hypointense on T1-W, without peripheral oedema and mass effect (*figure 1A*). Interictal ^{18}F-FDG PET/CT demonstrated a zone of hypometabolism localized in the left mesiotemporal region (*figure 1C, D*).

Presurgical neuropsychological assessment revealed verbal memory impairment, dysexecutive syndrome, and decline in confrontational naming.

A left anterior temporal lobectomy with amygdalohippocampectomy including lesionectomy was performed (*figure 1B*). Histopathological examination of the resected specimen revealed the presence of multiple discrete or coalescent nodules of vacuolating tumour cells (MAP2+, chromogranin A+, synaptophysin+, NF-, NeuN-, GFAP-, Ki-67-), CD68+ microglial elements, alongside rare CD34+ dendritic cells (*figure 2A, B*).

The patient was rendered seizure-free following surgery (follow-up of 24 months). Postoperative neuropsychological reassessment demonstrated additional decline in verbal memory and nomination, while other cognitive functions were maintained at preoperative levels.

Discussion

Based on a recent case series (Nunes *et al*., 2017), although pathological confirmation was lacking in the majority of analysed subjects, neuroimaging features of MVNT with subtle variations were characterized as almost pathognomonic. These characteristics consist of a group of multiple, tiny, discrete, and sharply demarcated intra-axial nodules, ranging from 1 to 5 mm, in the supratentorial lesions located on the inner surface of the cortex. These nodules are hyperintense on T2-W (and visible on FLAIR) and hypointense on T1-W spin-echo sequences, and rarely show progression on MRI follow-up. In addition, the pathologist's examination allows accurate diagnosis due to the characteristic microscopic appearance and immunohistochemical profile (Pekmezci *et al*., 2018). MVNTs are of particular interest to the clinician/epileptologist, not only because of the frequent association with epileptic seizures, but also as an operatively treatable cause of epilepsy.

A total of 96 cases (including the current case) have been described in the literature to date (Ratilal *et al*., 2007; Huse *et al*., 2013; Bodi *et al*., 2014; Fukushima *et al*., 2015; Nagaishi *et al*., 2015; Yamaguchi *et al*., 2016; Alsufayan *et al*., 2017; Badat *et al*., 2017; Cathcart *et al*., 2017; Gökçe, 2017; Monté *et al*., 2017; Nunes *et al*., 2017; Gonzalez-Quarante *et al*., 2018; Kapucu *et al*., 2018; Lobo and Srinivasan, 2018; Pekmezci *et al*., 2018; Thom *et al*., 2018) (*supplementary table 1*), of which 37 were histopathologically verified (HV) (38.54%). A slight female predominance was noticed in both non-HV and HV cases (M:F=2:3 and M:F=9:11, respectively). Mean age was 40 in both groups (range: 6-71 years) at the time of initial diagnosis. Although most of the described cases implicate adulthood-onset epilepsy

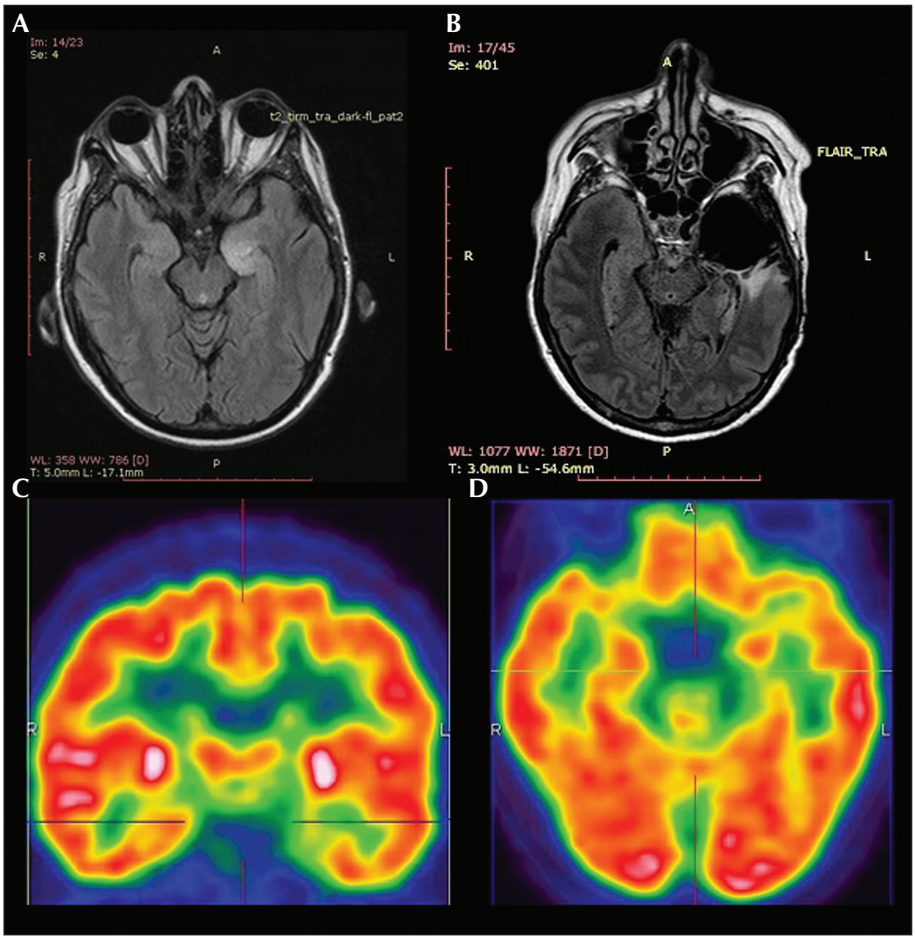

Figure 1. Neuroimaging of MVNT. (A) Preoperative brain FLAIR MRI in axial plane showing a cluster of nodular hyperintense lesions in the left parahippocampal gyrus, extending to the hippocampus and amygdaloid body; (B) postoperative brain FLAIR MRI in axial plane; (C, D) ^{18}F-FDG PET showing a hypometabolic zone in the left mesiotemporal region in coronal (C) and axial (D) plane.

(median: 32.5 years), the index seizure can occur even before the age of six, as well as in senium, after 65 years of age. Potential triggers prior to epilepsy onset that may point to the "second-hit" hypothesis are not reported in the current literature.

The most common tumour location was the temporal lobe (44.79%; including overlapping localizations), followed by the parietal (30.2%), frontal (28.12%), and occipital (10.42%) lobe, while the presence of MVNT in the insular region remains to be described. MVNT of temporal localization also predominates in HV cases (75.67%; including overlapping localizations), followed by frontal localization (10.81%). Lesions were more often localized to the left hemisphere in the non-HV group (54%), compared to the HV group (51%) in which right lateralization discreetly predominated.

In total, 39 patients (40.62%; 26 HV) were diagnosed with epilepsy (including two probable cases without an established diagnosis of epilepsy, but clinically presenting with repeated paroxysmal, stereotypical, and short-lasting events) (*supplementary table 2*). This finding partially contradicts the earlier assumption that MVNTs are mainly asymptomatic lesions which could be "leave me alone" entities (Nunes *et al*., 2017). However, complaints from MVNT patients without epilepsy may be due to variable neurological symptoms, moreover, the topographical association with tumour location is poor. Acute or chronic headache was the second most frequent complaint leading to a positive MRI finding (31.25%). According to the few available descriptions of headache characteristics, these complaints do not meet the criteria for headache attributed to intracranial neoplasia, thus MVNTs could be considered as incidental findings rather than a location where lesions lead to secondary intracranial hypertension headache (Headache Classification Committee of the International Headache Society, 2013). Additionally, assuming that symptomatic patients represent the tip of the iceberg, the majority of cases remain under the radar and are asymptomatic and probably never diagnosed. Therefore, epilepsy is probably less frequently associated with

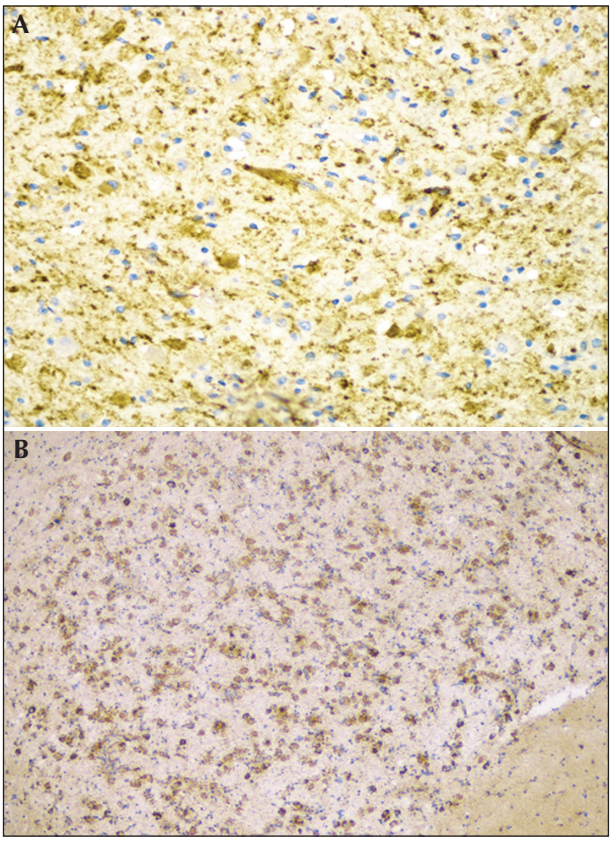

Figure 2. Histopathological features of MVNT. Positive immunohistochemistry for synaptophysin (A) (x200 magnification) and chromogranin A (B) (x40 magnification) in a nodule of tumour cells.

MVNT compared to DNET and other low-grade epilepsy-associated tumours (van Breemen *et al*., 2007). Nevertheless, some cases of MVNTs could have been misdiagnosed as other more prevalent lesions that share histological similarities, based on epilepsy series (Thom *et al*., 2018).

Considering seizure semiology, temporal lobe tumours (the most common [71.79%] localization in MVNT and epilepsy cases) presented with epigastric and *déjà vu* aura, as well as automotor and dialeptic seizures. Seizure semiology is mostly omitted based on frontal (15.38%), parietal (23.08%), and occipital (2.56%) published cases.

The most frequent EEG finding was localized slow activity (46.67%). Ipsilateral or bilateral epileptiform activity was recorded in five cases, including our case (13%). In two cases (including the present case), the ictal onset zone was present in the lobe in which the lesion was situated. The effect of antiepileptic drug therapy was unclear as relevant data was lacking (data was not available in 31/39 cases). Pharmacoresistance was noted in only seven cases (including our case).

Table 1. Surgical treatment of epilepsy patients with MVNT and postoperative outcome (Engel Epilepsy Surgery Outcome Scale).

Type of surgery	Outcome (Engel Epilepsy Surgery Outcome Scale)
Resection 21/39 (53.85%)	I. 13 (76.47%) II. 1 (5.88%) III. 2 (11.76%) IV. 1 (5.88%)
Subtotal 4/21 (19.04%)	I. 2 (66.66%) IV. 1 (33.33%)
Gross total 6/21 (28.57%)	I. 4 (80%) III. 1 (20%)
Wide (lobectomy *etc.*) 11/21 (52.38%)	I. 7 (77.78%) II. 1 (11.11%) III. 1 (11.11%)
Biopsy 2/39 (5.13%)	
None 13/39 (33.33%)	
No data 3/39 (7.69%)	**No data** 4/21 (19.05%)

MRI features in our patient are concordant with existing descriptions in the literature (Alsufayan *et al*., 2017; Nunes *et al*., 2017). In addition, we provide interictal ^{18}F-FDG PET/CT of MVNT (described previously by Nunes *et al*. [2017]), revealing a hypometabolic zone in the tumour area. Although this finding may not be typical, it may be potentially beneficial for the detection of subtle lesions that are overlooked on MRI.

Epilepsy surgery was the main indication for surgical intervention in patients with MVNT (75%). Three different surgical strategies were applied: subtotal resection of the lesion (19%), gross total resection of the lesion (28.6%), and wide resection (52.4%; lobectomies were most commonly performed) (*table 1*). The average follow-up period was 34 months (range: 3-168). The majority of patients who received surgery were rendered seizure-free (Engel Class I outcome: 76.47%). All types of resections similarly prevented relapses. In general, temporal lobe resections due to MVNT have approximately the same success rate (70-80%) as temporal resections regardless of pathology. Possible reasons for the surgical failure in three patients might be limited resection (not involving potentially sclerotic hippocampus) or the multifocal origin of seizures (Huse *et al*., 2013; Bodi *et al*., 2014; Thom *et al*., 2018).

Pathohistological (morphological and immunohistochemical) presentation of the tumour in our case did not differ from those described in the literature (Huse *et al*., 2013; Bodi *et al*., 2014; Fukushima *et al*., 2015; Yamaguchi *et al*., 2016). The presence of CD34+

stellate-like cells (frequently seen in seizure-related lesions) within MVNTs could be responsible for the potential epileptogenic nature of these lesions (Cathcart *et al*., 2017).

MVNTs, with an indolent course and resembling both malformative and neoplastic processes, combine a focal developmental anomaly and a low-grade tumour (Thom *et al*., 2018). Although the existing association between MVNT and epilepsy does not necessarily indicate causality, the ictal EEG findings and the high percentage of successful resections may be key to understanding MVNT as undisputed epileptogenic lesions. Large series are required for a more detailed clinical and epileptological characterisation of patients with MVNT. □

Supplementary data.
Supplementary figures and tables are available on the www.epilepticdisorders.com website**.**

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What does MVNT stand for?

(2) To which group of tumours does MVNT belong to according to the 2016 World Health Organization Classification of Tumours of the Central Nervous System?

(3) What is the typical MRI presentation of MVNT?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".