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CALCIFYING PSEUDONEOPLASM OF THE NEURAXIS (CAPNON) ASSOCIATED WITH DRUG-RESISTANT EPILEPSY (DRE): A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract:

Background: Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare slow growing lesion with approximately 114 cases reported around the world. The pathophysiology still uncertain and incomprehensible. It is occurring either within the skull or within the spine. It has a various presentation clinically, and some variation radiologically and in histopathological findings. Case description: we present a case of 14 years old female patient, presented in ER as recurrent seizures case. CT done for her showing left temporal calcified lesion. Admitted with seizures for multiple time, seizures were reoccurred despite medication even with increasing the dose. Further imaging studies was done, and the diagnosis of CAPNON has become more likely. Treated by surgical resection. Conclusion: Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare CNS lesion had an increasing in number of reported cases, thus consider it in the deferential diagnosis of calcified lesion of CNS should be taken. Further studies with same or new tools is necessary to know the origin of the lesion since its pathophysiology still incomprehensible. Follow up with the patients after management may be useful in developing a better therapeutic option.

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1- INTRODUCTION:

Calcifying pseudoneoplasm of the neuraxis (CAPNON). A rare slow growing benign lesion, more in male gender (1.92:1), with mean age around 45 years old and range between 6–90 years old, fifty percent of them have been reported in age between 40 and 60 years [1,9,12]. First description was in 1922 by Miller as "intracranial calcification" [10] and it reported in 1978 by Rhodes and Davis as "An unusual fibro-osseous component in intracranial lesion"[2,5].

Radiologically appearance interferes with many common CNS tumors, especially Meningioma. CAPNON can be seen intracranial and intraspinal (in the spine). The lesion features on radiological studies such as CT and MRI, are important tool to reach diagnosis. It is rather extra-axial lesion or intra-axial lesion [4]. But overall, confirming diagnosis depends on histopathology [11, 13].

Clinically its mimic neurological diseases with manifestation related to compression, irritation, infection and vascular lesions (last two are more with intra-axial) [5]. Patients generally may present by seizures, headache, dizziness, limb paresis, abnormal gait and pain which is the commonest symptom of intraspinal CAPNON [3].
CAPNON seem to be curative by surgical resection. Recurrence after surgical resection is not significant (93.7% in intracranial CAPNON and 92.3% of intraspinal CAPNON, including cases treated with incomplete resection) [1].

Because this lesion is an incomprehensible and can occur anywhere along the neuraxis; it has a clinical and radiological variation. By combining these factors, reaching the diagnosis becomes a challenge, and according to a study of reported case in 2018, diagnosis of CAPNON is still a challenge [6].
This study takes its importance as an attempt to raise the level of knowledge about the lesion and diagnostic methods since there is a lack of studies. Numbers of CAPNON cases reported including this case, are approximately 115 reports of CAPNON to date to our knowledge [7-9,18].

2- CASE PRESENTATION:

A 14 years old girl presented to emergency department (ED) with active seizures, treated and discharged due to legibility issue. She is a known case of epilepsy since she was 4 years old on Depakene and not compliance to medication with history of recurrent seizures in childhood. Her medication changed to Keppra 500mg PO BID. CT brain done showing calcified lesion in the left temporal.

After one week she re-presented with history of generalized tonic-clonic seizures for 3 times with left eye gaze and swallowing gestures, each episode lasting for less than a minute and frequent almost every thirty minutes, consciousness is regained in between attacks. She seized in ED, received Diazepam 5mg IV and loading phenytoin 600mg IV and she back to her baseline. Neurosurgery department admit her, and in the assessment of her seizures it was in the form of up rolling eyes and urinary incontinence associated with jerky movement observed in the right side, lasting for a few seconds and then resolving without returning completely to her baseline.

In examination, she was confused and not oriented. She was not responding commands, moving all limbs spontaneously. Eye bobbing was witnessed with eyelid twitching. The seizure semiology was changing, she developed head turning to the right and fencing posture. Other times she would have mouth smacking. In between the attacks she would not regain consciousness. She had 4 attacks. Lorazepam 8mg was given over 2 doses 1 minute apart (4mg at a time), respiratory status was monitored throughout with no sign of depression. The seizures persisted despite that, and despite Keppra 1g loading IV giving. Glasco Coma Scale (GCS) was 11/15. Patient shifted to ICU to intubate her and start sedation on midazolam plus fentanyl. The impression was status epilepticus.

CT brain without contrast showing left temporal lobe calcified and lobulated mass measures 3.5 × 4.5 × 3.5 cm Anterior-Posterior (AP), transvers (TR) and craniocaudal (CC) dimensions (Fig. 1).

After two days, patient develop abnormal behavior with alter loss of consciousness, and sometimes screaming and shouting. She was vitally stable, afebrile and GCS of 15/15. She had a stair attack with no response to commands, unpurposeful bizarre movement and trying to get out of the bed, with left non forceful movements that last few second then aborted spontaneously, followed by mild post ictal confusion. In examination, she was sleepy and cooperative, but there are antigravity symmetrical reflexes. She received Keppra 1.5g loading IV and increasing the dose of Keppra to 750mg PO BID.

MRI brain with and without contrast done showing solitary left medial temporal lobe lesion measures 4 × 3 × 2.3 cm in its maximum diameter, that demonstrate heterogeneous signal intensity in T2-weighted imaging (T2WI) with rim of signal loss, blooming on Susceptibility-weighted imaging (SWI), heterogenous enhancement (Fig. 2).

One month later, the patient underwent left Pterional craniotomy transcortical -inferior temporal gyrus- and excision the left temporal lobe calcified mass. Intraoperatively, corticotomy done through the inferior temporal gyrus with subpial dissection the tumor encountered 1 cm deep. Surgeon report that the lesion was easily suckable, eggshell consistency and moderate bleeding. Mesial temporal lobe was reached and excised with the temporal pole, she received 1-unit packed RBCs plus 1L crystalloids. Estimated blood loss (EBL) is 400 ml. Postoperative, there were no significant complication, CT after the operation demonstrate expected postoperative changes with residual part of the tumor and interval development of intraventricular hemorrhage with no hydrocephalus or herniation and this managed by extubation, putting the drain on thumb pressure and giving dexamethasone 3mg IV QID.

Histopathology report a specimen of: (1) calcified tissue in frozen section, (2) calcified tissue, (3) mesial temporal tissue (adjacent to tumor) and (4) the involved temporal pole. The calcified tissue (2) was consist of multiple fragments of grey-tan tissue measuring 7.5 × 5 × 1.56 cm in aggregate with calcification were the mesial temporal tissue (3) was consist of 2 fragments of grey-tan soft tissue measuring 1.7 × 1.3 × 0.4 cm in aggregate, and the involved temporal pole was consist of 3 fragments of grey-tan soft tissue measuring 3 × 1.5 × 0.4 cm in aggregate.

The calcified tissue and mesial temporal tissue (1,2 and 3) it shows extensive calcified brain and choroid plexus tissue consistent with calcifying pseudoneoplasm of the neuraxis (CAPNON), There was no evidence of vascular malformation or neoplastic tumor. In the involved temporal pole (4) there was subpial Chaslin's gliosis which is secondary to epilepsy; otherwise unremarkable.

CT brain without contrast after two day of surgery showing mild left sided intra-ventricle hemorrhage are associated with a mild hydrocephalus with interval resolution of the right sided intraventricular hemorrhage. No newly seen acute insults (Fig. 3).

10 days after surgery, MRI with IV contrast done demonstrating the large left temporal lobe surgical cavity with surrounding peripheral and suspicious nodular enhancement more pronounced along the superior inner aspect, the largest measures 9 × 5 mm in diameters in the temporal surface, likely representing residual tumor tissue.

16 days after surgery, patient came with 3 attacks of generalized tonic-clonic seizures, she wasn't compliance with her medication. She feels rigors before the seizure. No visual or auditory symptoms, and no numbness. She restarted on her medication.

22 days after surgery, she develops an attack of partial seizure involving jerky movement of the right upper limb, aborted spontaneously. Changing her medication to Keppra 1.5g BID, Tegretol 400mg BID, and stop Lamotrigine.

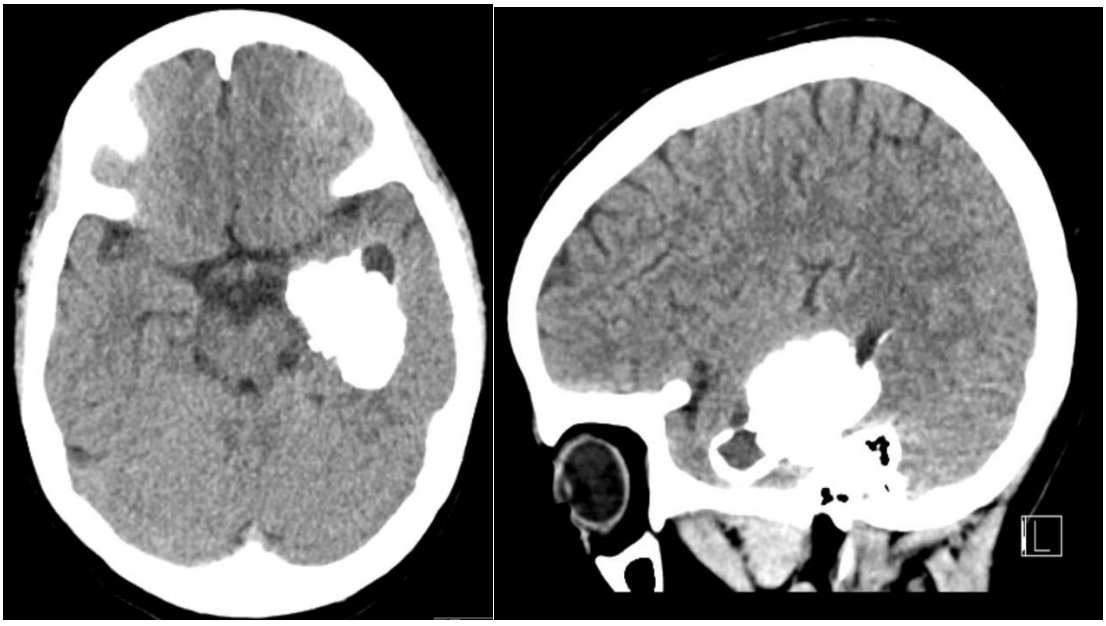

Fig. 1 There is an irregular macrolobulated heavily calcified mass with a few areas of hypodense components noted in the left temporal lobe which is inseparable from the left temporal horn of the left lateral ventricle. However, no significant associated cerebral edema, ventricular dilatation or sulcal effacement are noted. The mass measures 3.5 x 4.5 x 3.5 in the transverse, AP and CC dimensions.

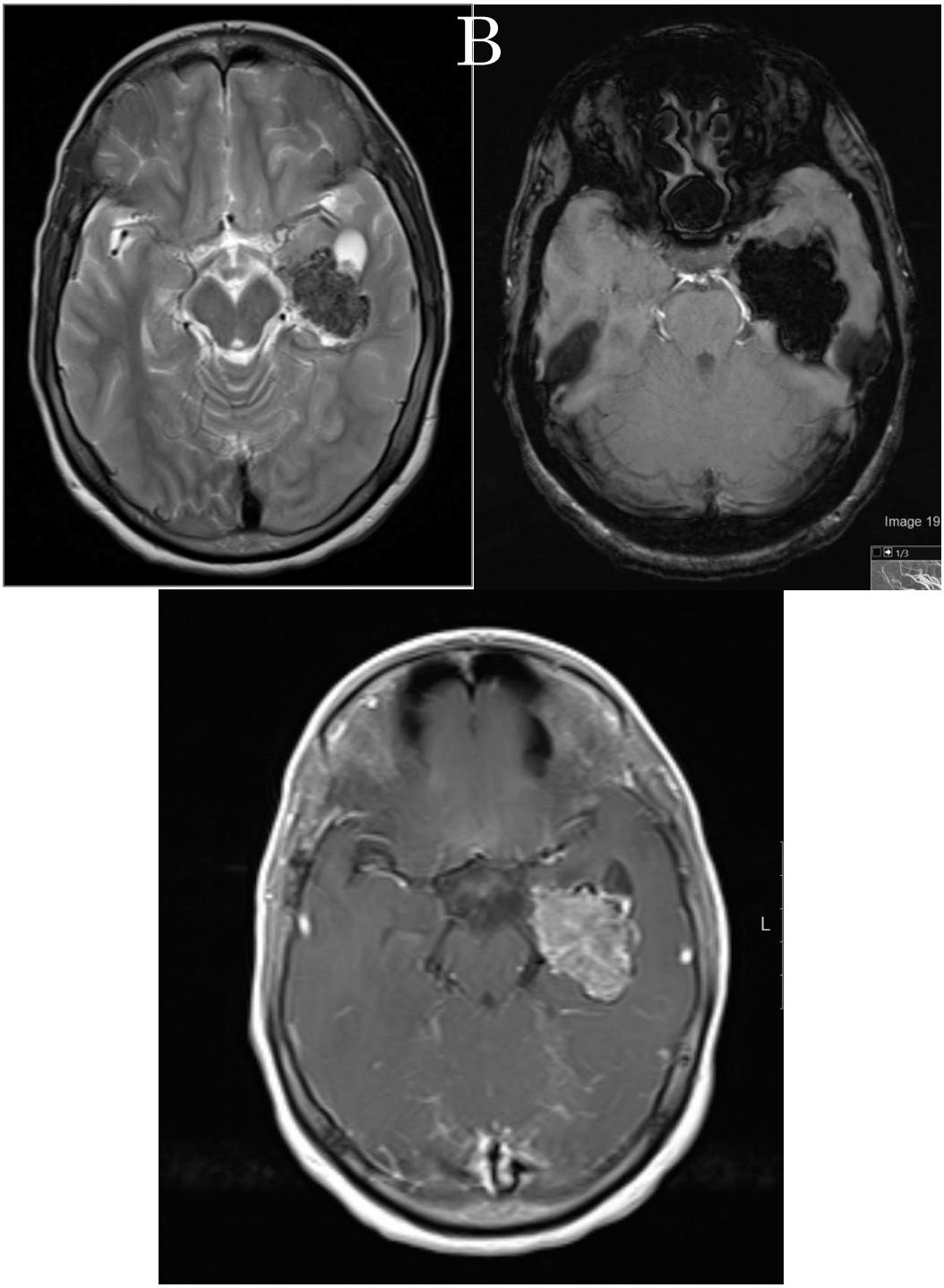

Fig. 2 Solitary left medial temporal lobe lesion measures about 4 x 3 x 2.3 cm in its maximum diameters, that demonstrates heterogeneous signal intensity in T2WI (A) with rim of signal loss and blooming on SWI (B) heterogeneous enhancement on T1 post contrast (C). No significant surrounding edema.

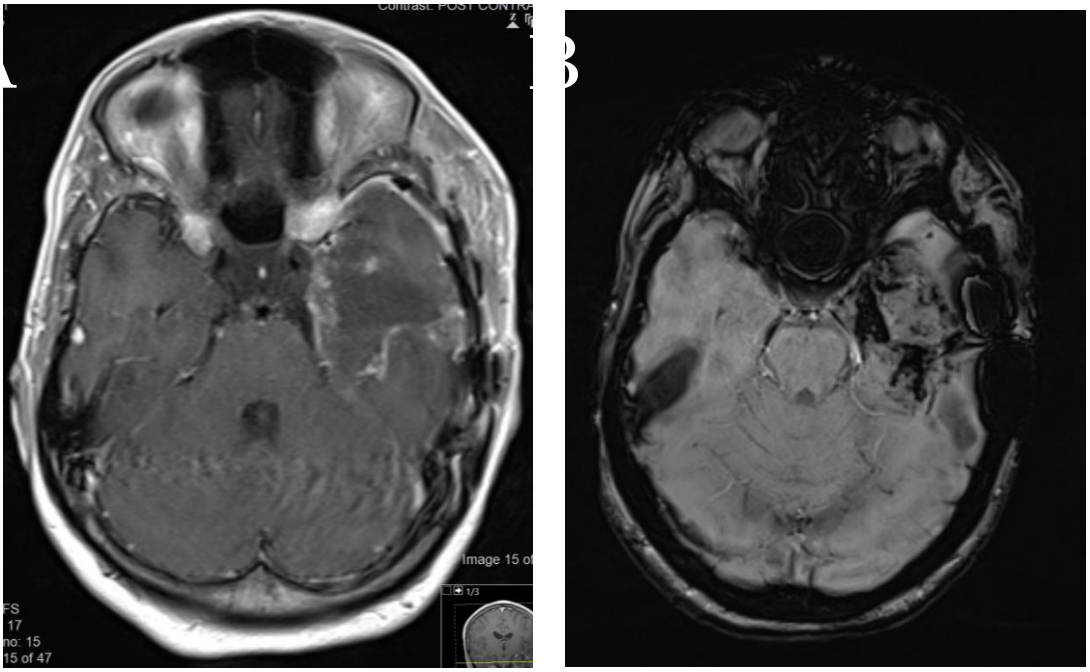

Fig. 3 Post-operative images
Post contrast T1 image (A) show a large left temporal lobe surgical cavity with surrounding peripheral and suspicious nodular enhancement more pronounced along the superior inner aspect, the largest measures 9 x 5 mm in diameters in the mesial temporal surface, likely representing residual tumor tissue.
SWI image (B) reveal multiple blooming foci of remote blood degradation products without corresponding conventional signal intensity seen in the operative bed. Dependent blooming signals of remote blood also identified with the left lateral ventricle.

3- DISCUSSION:

Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare disease with approximately 114 cases reported worldwide, we count the new reported cases after "Barber SM" study (see table 1). [8,18] It is slow growing; the progression takes 2-12 years [15]. And it is occurring anywhere along the central nervous system and thus the clinical presentation is variable based on the location and the size of the lesion. According to the reported cases, there are two main location of the lesion: intracranial or intraspinal, numbers of cases were 72 and 42 Respectively. [18] It can present in multiple lesion but no report to date for presence in both locations (intracranially and intraspinal) to our knowledge [3]. Most of intraspinal cases were in epidural space. [19]

So far, based on the information available from the studies, it is believed that the lesion is caused as a response to trauma, infection, inflammation and neoplasm. [11]

Until now, only 3 cases of CAPNON associated with neoplasms, and those neoplasms are ependymoma, dysembryoplastic neuroepithelial tumor (DNET) and WHO grade II meningioma. [14]

- Clinical presentation

Commonest clinical presentation of CAPNON can be divided by the lesion location into: The most common presentation of intracranial CAPNON which is seizure followed by headache. Intracranial CAPNON presentation also include cranial nerve palsy, dizziness, facial pain, loss of vision or hearing and ataxia.[18] The other division is intraspinal CAPNON which most commonly presented by pain that varies depending on the anatomical location and the size. The pain could be a local pain (commonly in neck and lumber) or radiculopathy. Intraspinal CAPNON also can present by myelopathy and cauda equina syndrome. [3,9,13,18] In general, some cases were discovered incidentally or found on autopsy. [14]

- Radiological features

Most of the cases of CAPNON, in CT the lesion appears as a solid hyperdense mass, and on both T1-weighted and T2-weighted MRI it characteristically shows a well-defined uniform hypointensity lesion, with no or limited surrounding edema. Only rim or serpiginous internal enhancement with contrast [1,5,9]. There were some reports of isointensity CAPNON lesions on both T1 and T2 weighted MRI. [17] To differentiate CAPNON radiologically, several lesions should be considered depending on the location. In case of intracranial and extra-axial lesions such as meningioma, chordoma,

chondrosarcoma, schwannoma, hemangiopericytoma, metastases and neurocysticercosis should be considered. In case of intracranial and intra-axial: ganglioglioma, oligodendroglioma, cavernous malformation and tuberculosis should be considered. [9,11,14]

- Histopathology

Typical histopathological features of CAPNON include chondromyxoid matrix in nodular pattern, spindle and epithelioid cells palisading around a chondromyxoid matrix, these are considered as distinctive CAPNON histological features, moreover there are other features including fibrous stroma in a variable amount, foreign-body-type reaction with giant cells, psammoma bodies and osseous metaplasia. It is not necessary that they all exist in one lesion [5,7,17]

The most common immunohistochemical stain findings are: (1) positive of epithelial membrane antigen (EMA) and vimentin, (2) negative of glial fibrillary acid protein (GFAP) and of S-100 protein staining. [11, 20] Other findings include: Cluster of Differentiation 68 (CD68) in moderate numbers, positive macrophages and prominent astrocytic gliosis by GFAP. [18] The spindle cells have been found positive to osteocalcin. [21] Immunohistochemical not done for our case.

Deferential diagnosis on histopathological basis include: chordomas, chondroblastoma and infectious granulomatous diseases. [21]

- Management

Complete resection is the treatment of choice. Complete resection shows a good prognosis and improvement. Surgical resection considered as effective management for drug-resistant seizures associated with CAPNON. [8,11] In our reported case, the patient doesn't show improvement regarding epilepsy since the patient still suffering from epileptic seizures. This could be due to the incomplete resection as the imaging studies representing a residual part of the tumor, or she is not compliance with medication, or the control dose of antiepileptic drugs is not achieved yet. Previous reports of CAPNON associated with epilepsy show that cases treated by complete surgical resection (82.4%) and by incomplete resection (17.6%), most were seizure-free. There was only one case with seizure remaining and it was treated by complete resection. [8]

Only three cases showing disease recurrence so far. Two of them were occurring after treated by incomplete resection, they were in both locations of CAPNON, intracranial (at the base of the skull) and intraspinal (intraosseous axial lesion). [1,14] The third one was in 2018, located in the frontal lobe and reoccurring after total resection. [15] Therefore, they recommend a maximum resection including an unidentified agent that may cause the regrowth and periodic follow up is necessary to avoid recurrence. Also, they recommend using both surgical and medical management for CAPNON especially in cases cannot be resected completely.
Medical management considered to control the progression of the lesion. Indomethacin is an example of medical treatment; it was administered for intraspinal (thoracic) CAPNON and result in resolving the lesion. [15,16] Also there was a failure of medical treatment by steroids in " Eric S. Nussbaum" study. [17]

4- CONCLUSION:

Calcifying pseudoneoplasm of the neuraxis (CAPNON) is a rare CNS lesion which had an increase in the number of reported cases, thus considered in deferential diagnosis of calcified CNS lesion should be taken. Reaching the correct diagnosis will prevent medical team from taking remedial steps in management that are useless or harm. Further studies with same or new tools is necessary to know the origin of the lesion since its pathophysiology still incomprehensible. Also, excluding another neoplasm may be associated with CAPNON should be including in work up. Follow up with the patients after management may be useful in developing better therapeutic options.

Case	Author	Year	Age (years)	Sex	Presenting Symptoms	Location	Contrast Enhancement	Oedema	Treatment	Post operative F/u (months)	Clinical Outcome	Recurrence
62	Farahnaz B. ZEREHPOOSH [22]	2018	25	M	incidental	left temporal	ND	None	Surgical resection	36	Stable	None
63	Halil O. Peker [6]	2018	58	F	dizziness	lateral cerebro-medullary junction	ND	+	Surgical resection	2	Dizziness resolved	Recurrent at 1 year
64	Michael A. Paolini [14]	2018	17	M	seizure	left posterior quadrant	+	+	Surgical resection	ND	ND	ND
65	Eric S. Nussbauma [17]	2018	39	F	sudden hearing loss	mastoid	+	None	Surgical resection	ND	Expected hearing loss	ND
66	Timothy C. Blood [23]	2018	65	F	Hearing loss	right frontal	+	ND	None	NA	Asymptomatic	NA
67	Michael M. Safaee [24]	2018	8	M	seizure and alteration in consciousness	right frontal	+	+++	Surgical resection	8	Improvement of oedema + weaned from anticonvulsants with no seizure	None
68	Mathilde Duchesne [25]	2018	26	F	seizure	left frontal	ND	+	Surgical resection	45	No seizures	None
69	Akira Watanabe [15]	2018	40	F	excessive somnolence	right frontal	ND	+	Surgical resection	144	ND	Recurrent at 14 months
70	Pithon R. Fonseca [11]	2019	17	M	seizure	left frontal	None	Minimal	Surgical resection	24	Stable	None
71	Yuta Tanoue [8]	2019	52	M	drug-resistant epilepsy	left temporal	ND	None	Surgical resection	12	No seizures	None
72	Bhaskar Thakur [26]	2019	67	F	walking difficulty	cerebellum	ND	ND	Surgical resection	12	Improvement in gait, coordination and cognitive	None
73	Yahia Al-Zahrani	2019	14	F	Seizure	Left temporal	+	Minimal	Surgical resection	<1	Attacks of seizures	ND

Table 1. This include the new cases reported since Barber SM study [18]. These are all intracranial CAPNON cases reported in 2018-2019. There were no new intraspinal cases reported. **M**: Male, **F**: Female, **ND**: No Data, **NA**: Not Applicable

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