# Review of literature

We screened PubMed for other case reports of TSC patients with NMDARE using the terms “NMDA receptor encephalitis” in combination with “Tuberous sclerosis complex”, “subependymal giant cell astrocytoma”, “phakomatosis” or “neurocutaneous disorders” respectively but we did not find any case reported by these search terms.

In a next step we searched for reports of brain tumo(u)rs and NMDARE and found one case of neurofibromatosis type 1 by screening for “brain tumors” and “NMDA receptor encephalitis” but no other case of an associated neurocutaneous syndrome (1).

Further search items were “NMDA receptor antibodies” and “brain tumo(u)r” and “NMDA receptor encephalitis” and “paraneoplastic”. We identified four case reports describing brain tumors in association with NMDA receptor encephalitis. The full text of the case reported by Fujii et al. was only available in Japanese, so we were limited to information given in the abstract (2).

A case of a retroperitoneal ganglioneuroma and a metastasized neuroblastoma in a 20-month-old and a 3-year old boy with NMDARE were not included as both were no primary brain tumors (3).

In a third step we screened PubMed with search items of specific primary brain tumors, i.e. “glioma”, “astrocytoma”, “glioblastoma” and “NMDA receptor encephalitis”, which only added one single case of a pilocytic astrocytoma (4).

We also checked for cases of “meningioma”, “oligodendroglioma”, “ependymoma”, “dysembryoplastic neuroepithelial tumo(u)r”s, “medulloblastoma”, “(vestibular) schwannoma”, “craniopharyngeoma”, “plexuspapilloma” or “glioneuronal tumo(u)rs” and NMDARE could not find any further case of a primary brain tumor, while there was one case of a perineal schwannoma in a 75-year old male (5).

The clinical characteristics of all six cases including the current one are summarized in Table 1. Treatment and outcome are depicted in Table 2 while Table 3 presents the laboratory results.

The coexistence of primary brain tumors and NMDARE is meaningful for clinicians, as both entities share phenotypic features (e.g. seizure, behavioral changes) while therapeutic options are quite different. Nonetheless, the combination of NMDARE and brain tumors still seems to be rare if we take into account that more than 800 cases of NMDARE were quickly reported after discovery (8,10).

It is possible that rare tumors associated with NMDARE are more likely to be published – so that the real percentage of brain tumors in NMDARE may be even lower. Conversely, neuropsychiatric symptoms in patients with brain tumors are likely commonly attributed to the tumor itself or to side effects of therapy, and NMDAR antibodies are rather not tested. Thus, secondary NMDARE may be underdiagnosed in such constellations. Although data are too limited to draw any definite conclusions, it is remarkable that all brain tumors of adult patients described are of (at least suspected) glial origin, while we did not find any case report of meningiomas, medulloblastomas, neuroepithelial tumors or glioneuronal tumors in patients with NMDARE, which may support the idea of a causal connection between both entities.

**Table 1: Clinical characteristics of cases with brain tumors and NMDA receptor encephalitis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Case | Tumor type | Gender/  Age |  | Specific  characteristics | Psychiatric symptoms | Other symptoms |
| (2) | Glioblastoma | f,54 |  | Co-occurence with  teratoma | n.a. | Complex-partial seizures  Impaired consciousness |
| (6) | Oligoastrocytoma | f,29 |  |  | Psychosis | Complex partial seizures  Déjà-vu  Blurred vision |
| (7) | Hippocampal mass | m,18 |  | Unknown etiology | Depressive symptoms  Auditory hallucinations  Relationship breakdown  Intentional overdoses | No other symptoms (isolated psychiatric) |
| (8) | Pineal dysgerminoma | m,9 |  | Removed months before NMDARE onset.  Teratoma component | Behavioural disturbances  Anorexia | Sleeping disorders |
| (4) | Pilocytic astrocytoma (pons) | f,32 |  |  | Agitation  Aggressiveness  Visual hallucinations  Paranoid delusions | Working memory deficits  Tonic-clonic seizures  Dyskinesia  Choreaathetosis  Respiratory crisis  Severe coma |
| (9) | Frontal parietal astrocytoma WHO II-III | m,67 |  |  | No psychiatric symptoms | Frequent partial seizures |
| Ihl et al. | SEN DD SEGA | f,35 |  | TSC related | Auditory hallucinations  Suicidal thoughts | No definite non-psychiatric symptom |

f = female, m = male, n.a. = not available, NMDARE = NMDA receptor encephalitis, SEN DD SEGA = differential diagnosis of subependymal node or subependymal giant cell astrocytoma, TSC = Tuberous sclerosis complex.

# Tables

**Table 2: Treatment and outcome of cases with brain tumors and NMDA receptor encephalitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Case | Tumor type | Surgical Treatment | Chemotherapy  Radiation | Immunosuppressives | Outcome |
| (2) | Glioblastoma  + ovarian teratoma | Removal of ovarian teratoma | n.a. | n.a. | n.a. |
| (6) | Oligoastrocytoma | Tumor removal | None | Steroid pulse therapy | Seizure-freedom after surgery -> Complete recovery |
| (7) | Hippocampal mass | None | None | 5 days of IVIgs for every relapse  Rituximab for maintainance | No further relapse under rituximab  Recovery to premorbid mental state within 4 days |
| (8) | Pineal dysgerminoma | Removal months before NMDARE onset | C + R | IVIgs,  Rituximab,  Cyclophosphamide. | Severe cognitive sequelae at 6 months  mRS 0 at 24 months |
| (4) | Pilocytic astrocytoma (Pons) | None | None | High-dose Prednisolone i.v.  IVIgs (3 cycles)  Rituximab (2 cycles)  Cyclophosphamide (2 cycles)  Plasma exchange (4 cycles à 5 sessions) | **Death** 14 months after NMDARE symptom onset |
| (9) | Frontal parietal astrocytoma WHO II-III | None | C + R | Dexamethasone i.v. (2 cycles)  IVIgs (2cycles)  Azathioprine | **Death** about 6 months after symptom onset |
| Ihl et al. | TSC-related brain tumors | None | None | Rituximab  Steroids | Relapsing-remitting ->  Suicide |

C = chemotherapy, IVIgs = intravenous immunoglobulins, n.a. = not available, NMDARE = NMDA receptor encephalitis, mRS = modified Ranking Scale, R = radiotherapy, TSC = Tuberous sclerosis complex.

**Table 3: Laboratory results of cases with brain tumors and NMDA receptor encephalitis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Case | Tumor type | Gender/  Age | CSF parameters | OB | NMDAR-antibodies (Serum) | NMDAR-antibodies (CSF) |
| (2) | Glioblastoma | f,54 | n.a. | n.a. | n.a. | n.a. |
| (6) | Oligoastrocytoma,  WHO II | f,29 | C: w.n.r.  P: w.n.r. | n.a. | Negative | 1:64 |
| (7) | Hippocampal mass of unknown etiology | m,18 | C: Lymphocytic pleocytosis  P: n.a. | n.a. | Initially exclusively in serum. | Positive only later in  the course |
| (8) | Pineal dysgerminoma | m,9 | C: 0/µL  P: 0.43 g/L | No OB | n.a. | n.a. |
| (4) | Pilocytic astrocytoma | f,32 | w.n.r. | n.a. | Positive (no titre given) | Positive (no titre given) |
| (9) | Astrocytoma, WHO II-III | m,67 | C: 4/µL  P: 0.45 g/L | n.a. | 1:32 | 1:10,  2 months later 1:32 |
| Ihl  et al.\* | TSC-related brain tumors | f,35 | C: 3/µL  P: 0.35 g/L | No OB | 1:10 000 | 1:3 |

CSF = cerebro-spinal fluid, n.a. = not available, OB = oligoclonal bands, \*parameters 4 months after clinical symptom, w.n.r.= within normal range, C = cells, P = protein.

# References of the Supplementary material

1. Encefalitis aguda mediada por anticuerpos contra el receptor ionotrópico de glutamato activado por N-metil-D-aspartato (NMDAR): análisis de once casos pediátricos en Argentina (Premio Benito Yelín) - Semantic Scholar [Internet]. [cited 2019 Jul 18]. Available from: https://www.semanticscholar.org/paper/Encefalitis-aguda-mediada-por-anticuerpos-contra-el-P%C3%A9rez-Ruggieri/13131811bd8cf3c3127b552463fc2aa296c9d167

2. Fujii H, Kubo S, Yunoki T, Sato K, Takamatsu K, Tanaka K, et al. [Glioblastoma with ovarian teratoma having N-methyl-D-aspartate receptor (NMDAR) antibody in CSF--a case report]. Rinsho Shinkeigaku. 2013;53(9):712–5.

3. Noguchi S, Kaga Y, Takahashi Y, Aoyagi K, Nakamura K, Kamiya Y, et al. [A case of recurrent paraneoplastic cerebellar ataxia with antibodies to GluR epsilon 2 causally related to ganglioneuroma]. - PubMed - NCBI [Internet]. [cited 2019 Jul 18]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Noguchi+AND+paraneoplastic+AND+NMDA

4. Beretta F, Aliprandi A, Di Leo C, Salmaggi A. A Case of Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated with Glioma of the Pons. J Clin Neurol Seoul Korea. 2019 Jan;15(1):125–7.

5. Viaccoz A, Desestret V, Ducray F, Picard G, Cavillon G, Rogemond V, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. Neurology. 2014 Feb 18;82(7):556–63.

6. Matsumoto R, Mikuni N, Tanaka K, Usami K, Fukao K, Kunieda T, et al. Possible induction of multiple seizure foci due to parietal tumour and anti-NMDAR antibody. Epileptic Disord Int Epilepsy J Videotape. 2015 Mar;17(1):89–94; quiz 94.

7. Warren N, Theodoros T, Blum S. Atypical N-methyl-D-aspartate receptor encephalitis and a hippocampal tumour. Aust N Z J Psychiatry. 2017;51(4):414–5.

8. Bost C, Chanson E, Picard G, Meyronet D, Mayeur M-E, Ducray F, et al. Malignant tumors in autoimmune encephalitis with anti-NMDA receptor antibodies. J Neurol. 2018 Oct;265(10):2190–200.

9. Lu J, Zhang J, Miao A, Yin J, Zhu D, Lin X, et al. Brain astrocytoma misdiagnosed as anti-NMDAR encephalitis: a case report. BMC Neurol [Internet]. 2019 Aug 28 [cited 2019 Nov 17];19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712735/

10. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013 Feb;12(2):157–65.