# 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 |  | Specificcharacteristics | Psychiatric symptoms | Other symptoms |
| (2) | Glioblastoma | f,54 |  | Co-occurence withteratoma | n.a. | Complex-partial seizuresImpaired consciousness |
| (6) | Oligoastrocytoma | f,29 |  |  | Psychosis  | Complex partial seizuresDéjà-vuBlurred vision |
| (7) | Hippocampal mass | m,18 |  | Unknown etiology | Depressive symptoms Auditory hallucinationsRelationship breakdownIntentional overdoses |  No other symptoms (isolated psychiatric) |
| (8) | Pineal dysgerminoma | m,9 |  | Removed months before NMDARE onset.Teratoma component | Behavioural disturbancesAnorexia | Sleeping disorders |
| (4) | Pilocytic astrocytoma (pons) | f,32 |  |  | Agitation AggressivenessVisual hallucinationsParanoid delusions | Working memory deficitsTonic-clonic seizuresDyskinesiaChoreaathetosisRespiratory crisisSevere 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 hallucinationsSuicidal 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 | ChemotherapyRadiation | 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 relapseRituximab 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 monthsmRS 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 | RituximabSteroids | 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 pleocytosisP: n.a. | n.a. | Initially exclusively in serum. | Positive only later in the course |
| (8) | Pineal dysgerminoma  | m,9 | C: 0/µLP: 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/µLP: 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/µLP: 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

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