

# ANXIETY SYMPTOMS MAY ALARM FOR LIFE-THREATENING MEDICAL CONDITION IN FEMALES: A CASE OF THE ANTI-NMDAR ENCEPHALITIS-ASSOCIATED WITH OVARIAN TERATOMA

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## INTRODUCTION

Anxiety is a symptom which arises across the variety of medical conditions starting from the key signs of reactions to acute stress toward accompanying severe organic brain disorders and somatic diseases (Takamatsu & Nakane 2022). Anxiety and brain fog have become increasingly prevalent during the COVID-19 pandemic, including vulnerable population-groups of females and pregnant women, which brought novel difficulties to the differential diagnosis, as well as understanding the underlying causes, triggers and deterioration of mental and somatic states (Burak 2023, Padila et al. 2021, Takamatsu & Nakane 2022). Anti-NMDA receptor (anti-NMDAR) encephalitis may manifest with anxiety and agitation symptoms, followed by confusion, motor, and other neuropsychiatric disturbances, thus, signalling about the development of the life-threatening state (Liu et al. 2022, Neerukonda et al. 2020). In women, anti-NMDAR-encephalitis is often associated with predisposing growth of ovarian teratomas, which can trigger the secretion of cross-reactive autoantibodies that bind to the NR1-subunit of NMDA receptors, and highlight the significance of considering its related risk-factors (Liu et al. 2022).

## CASE-REPORT

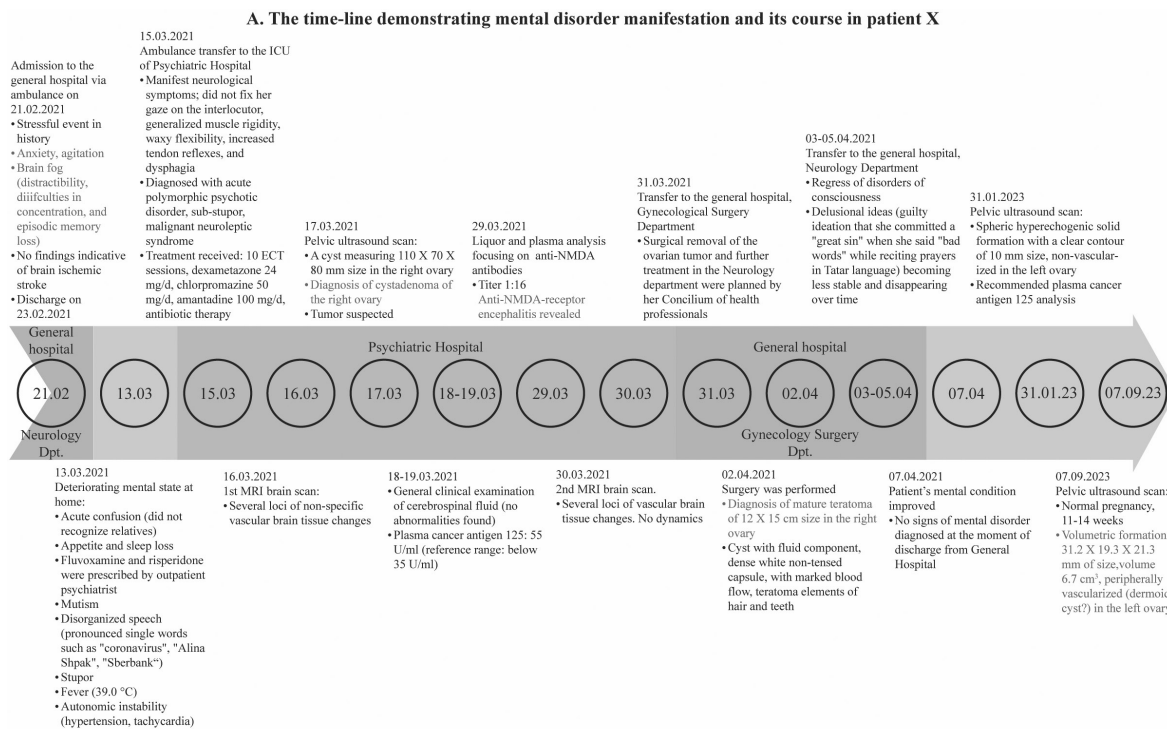
Here we report the case of female Patient X., born in 1993, who was transferred to the Psychiatric Hospital on March 15<sup>th</sup>, 2021 with a diagnosis: “Acute polymorphic psychotic disorder. Substupor. Malignant neuroleptic

syndrome” from Neurology department of General hospital (see Fig. 1A for detailed patient’s medical trajectory and course of her neuropsychiatric disorder). In her medical history she had an early autoimmune disorder of psoriasis, the delivery two years ago, and recent exposure to stressful event.

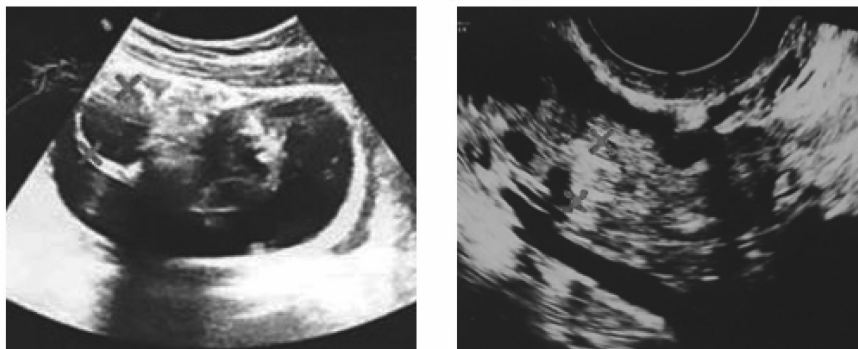
On February 21<sup>st</sup>, 2021 this young woman experienced anxiety, agitation, and brain fog symptoms, including distractibility, difficulties in concentration, and episodic memory loss. Mental state abruptly deteriorated by March 13<sup>th</sup>, 2021 with acute confusion, intermittent episodes of mutism and disorganized speech, as well as stupor, autonomic instability, and fever. Antipsychotic and antidepressant treatment had been prescribed, followed with the hospitalization to the Intensive Care Unit (ICU) of Psychiatric hospital, where neuroleptic malignant syndrome was suspected, and an appropriate treatment was administered (Fig. 1A).

In order to clarify the etiology of neuropsychiatric condition MRI brain scans, cerebrospinal fluid (CSF) analysis and pelvic ultrasound examination were performed. The right ovarian cystadenoma was identified, whereas no specific abnormalities were found in CSF and brain morphology. Online second expert opinion was arranged, and liquor analysis for anti-NMDA-receptor antibodies was recommended. Anti-NMDAR encephalitis was revealed (autoantibodies titer 1:16), and plasma cancer antigen-125 (55 U/ml) was found to be elevated.

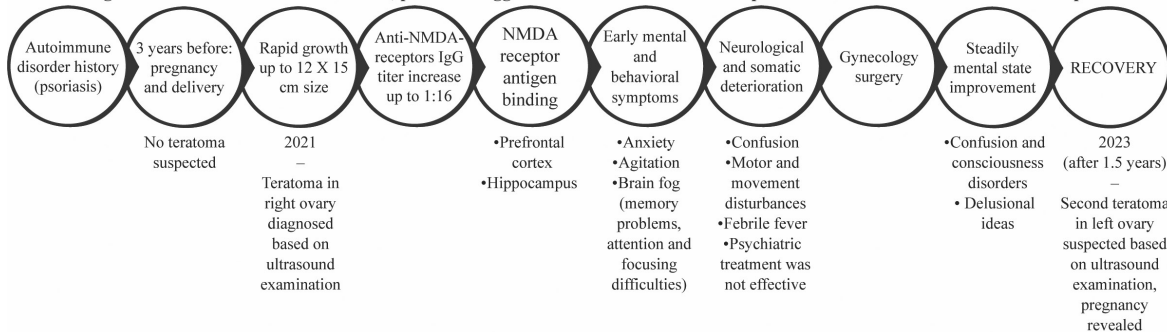
The surgery was performed in the Gynecological surgery department with dissection of mature vascularized teratoma including the elements of hairs and teeth, followed by the reduce of consciousness disorders,



### B. Pelvic ultrasound scans from 17.03.2021 (right ovary) and from 31.01.2023 (left ovary)



### C. Pathogenetic links between the risk factors, potential triggers and their causal relationships with mental and somatic conditions in patient X



### D. Key point message from the case of patient X for healthcare professionals

- Risk, predisposing factors and potential triggers to be considered:** female gender, history of autoimmune disorders, history of recent pregnancy and delivery
- First mental disorder signs and symptoms to be monitored:** anxiety, agitation, brain fog (in particular, deterioration of cognitive functions)
- Ultrasound examination-based screening in this category of patients should also focus on** the early detection of ovarian teratoma and its relapse

If mental condition (e.g., anxiety or brain fog) deteriorates or co-expresses with new neurological signs, **CONSIDER anti-NMDAR-encephalitis diagnosis**

**Figure 1.** Patient X's medical trajectory and course of neuropsychiatric disorders (A), pelvic ultrasound scans, demonstrating ovarian teratomas, in 2021 and 2023 (B), pathogenetic links between the risk factors, potential triggers and their causal relationships with mental and somatic conditions in patient X (C), and key point message based on the case of patient X for healthcare professionals (D).

Note: Dpt. – department; ICU – intensive care unit; NMDA – N-methyl-D-aspartate

intermittent delusional ideas occurrence and their disappearance over time.

The patient demonstrated full recovery from anti-NMDAR encephalitis and gynecological pathology over the following period until 2023. However, after 1.5 years the second teratoma in the left ovary during novel pregnancy has emerged (Fig. 1A and 1B). There were no any mental disturbances revealed at the moment of the second teratoma diagnosis.

## DISCUSSION

Understanding pathogenetic links between (i) risk factors and potential triggers (female sex, autoimmune disorder, recent pregnancy and delivery, ovarian teratoma, etc.), (ii) anti-NMDAR encephalitis, and (iii) non-specific symptoms of anxiety, brain fog as its early signs, and further full-blown psychotic, motor, consciousness, and neurological symptoms, can contribute to early detection and appropriate management of this potentially life-threatening condition (Fig. 1C) (Chahal et al. 2021, Chefdeville et al. 2019, Liu et al. 2022). Females are more prone to develop higher immune response and, thus, autoimmune disorders (e.g., psoriasis) partially due to higher X-linked susceptibility genes concentration located in both X chromosomes, compared to males (Du et al. 2014, Shankar 2020). Teratoma can trigger formation of autoantibodies that have cross-reactivity with NMDAR, and pregnancy and delivery are well-known risk factors for teratoma occurrence and growth (Chefdeville et al. 2019, Gu et al. 2021). All these factors have been presented at life timeline of patient X (Fig. 1A-1C).

## CONCLUSIONS

Such frequent co-occurrence of risk factors and potential triggers (female gender, history of autoimmune disorders, recent pregnancy and delivery), early developing development of non-specific mental disorder' signs (e.g., anxiety, agitation, brain fog, including deterioration in cognitive functioning) and progressing neuropsychiatric disturbances progression (e.g., consciousness disorders, psychotic, and neurological symptoms) should be taken into account to screen for anti-NMDAR encephalitis, and as well as pelvic ultrasound scan for ovarian

tumors examination should be routinely incorporated into management of this category of patients (Fig. 1D).

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**Ethical Considerations:** Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

**Conflict of interest:** Nothing to declare

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