Tacrolimus-induced cognitive impairment : a case report

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INTRODUCTION

Tacrolimus is an immunosuppressant used to prevent allogenic organ transplant rejection. It crosses the blood-brain barrier and inhibits calcineurin, a protein phosphatase highly expressed in the central nervous system (CNS). Tacrolimus is known for its organ toxicity, including neurotoxicity [1]. The following case illustrates that tacrolimus can lead to severe cognitive dysfunction, manifesting features akin to behavioral variant frontotemporal dementia (bvFTD).

CASE PRESENTATION

A 61-year-old man was hospitalized for of a vesicular rash on his left hemithorax and hyperactive delirium. Despite negative viral studies in blood and liquor, he was treated with IV acyclovir. The patient had a history of eosinophilic asthma and end-stage COPD for which he received a double-long transplant two years earlier and was taking tacrolimus at a variable dose. Post-transplant, he suffered from recurrent pneumonia and confusion. As his wife reported a progressive cognitive decline over the past two years, he was discharged to a neurorehabilitation clinic for further evaluation.

During his stay, the patient was disoriented in time and space. He sporadically experienced visual hallucinations. He felt mildly depressed and had recently resumed smoking. Rules about smoking lead to conflicts on the ward. His wife found him less empathic, more withdrawn and verbally aggressive. She reported an increased libido and problems with memory, sleep (insomnia) and basic ADL (mainly dressing and grooming). Difficulties with instrumental ADL (shopping and managing complex medication schemes) were also observed. Neuropsychological tests, including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), were administered and showed strongly deviating scores on visuo-spatial and executive memory, semantic fluency, attention and immediate and delayed recall [2]. The patient had no personal or family history of psychiatric or neurologic disorders.

Additional investigations were performed (Online Resource 1). No infectious, inflammatory, or acute metabolic abnormalities were detected in the blood; tacrolimus levels were repeatedly normal. Brain

MRI showed mild global cortical atrophy without structural abnormalities. FDG-PET scan of the brain revealed a mildly decreased metabolism in the frontal areas and precuneus (Fig. 1). Liquor analysis consistently showed normal glucose and protein. There was a mild lymphocytic pleiocytosis at the last two punctures of 10 and 8/mm^3 respectively which was attributed to the suspected herpes zoster rash, with previous punctures showing a normal cell count. Extensive screening for autoimmune, paraneoplastic, hematological or other infectious causes in the cerebrospinal fluid was negative. Biomarker profile was as follows: increased total and hyper phosphorylated tau, decreased amyloid-$\beta_{1\text{-}42}$ and amyloid-$\beta_{1\text{-}42/1\text{-}40}$ ratio. Genetic analysis of *C9orf72*, *GRN*, *MAPT*, *VCP* and *TBK1* did not show a known pathogenic variant.

The initial working diagnosis was an atypical presentation of a neurodegenerative dementia. The patient met the criteria for possible bvFTD: early behavioral disinhibition, apathy, loss of empathy, and increased cigarette consumption despite undergoing a double lung transplant [3]. The frontal hypometabolism on PET supported this diagnosis. The case was presented to the chief psychiatrist, who deemed a primary psychiatric disorder unlikely. A CNS infection or autoimmune disease were considered less likely given the functional decline over two years, the absence of related imaging or liquor abnormalities. Finally, because of the temporal association between the introduction of tacrolimus and symptom onset, a drug-induced cognitive deficit was considered. Although the patient was also taking tramadol and corticosteroids, these drugs were less suspect, as they had been used for over a year before the onset of cognitive dysfunction (see Online Resource 2 for full medication list).

Five weeks after admission to the clinic and in consultation with his treating pneumologist, tacrolimus was switched to cyclosporine. In just one week, the patient's clinical state improved remarkably. The RBANS was re-administered, showing normal results on language testing. There was an improvement in the other cognitive domains without achieving normal results (see Table 1). The MMSE-score increased from 20/30 to 27/30. Soon the patient recovered sufficiently to return home. Thirty months after discharge, the patient continues to do well and lives independently with his wife.

DISCUSSION

In this patient, the diagnosis of a drug-induced cognitive deficit was delayed due to the fluctuating severity of the symptoms and multiple hospitalizations for infection (a common cause of delirium). During the patient's stay in the neurorehabilitation clinic, the diagnosis was further delayed and complicated by abnormalities on FDG-PET scan and in the cerebrospinal fluid. The patient's biomarker profile was compatible with a diagnosis of Alzheimer's disease, but as it is known that the

CSF biomarker profile can be abnormal in people without cognitive complaints and the clinical profile of this patient was not typical for Alzheimer dementia, this finding can be interpreted as a preclinical/prodromal stage [4]. In retrospect the patient displayed some of the typical side effects of tacrolimus, namely insomnia, confusion and disorientation, speech abnormalities, depression, and psychotic features. Because of normal tacrolimus whole blood levels and brain imaging, the drug had not been withdrawn. Tacrolimus whole blood levels are not a good marker for drug-induced neurotoxicity: in a literature review by Luzzi et al. (2020), most cases had normal blood levels [5]. Many of them had nonspecific neuro-imaging anomalies, but this patient shows that brain MRI can also be normal.

CONCLUSION

Tacrolimus can induce neuropsychiatric symptoms mimicking bvFTD. Discontinuation of the drug should be considered when drug-induced dementia is suspected, even when blood serum levels and brain imaging are normal.

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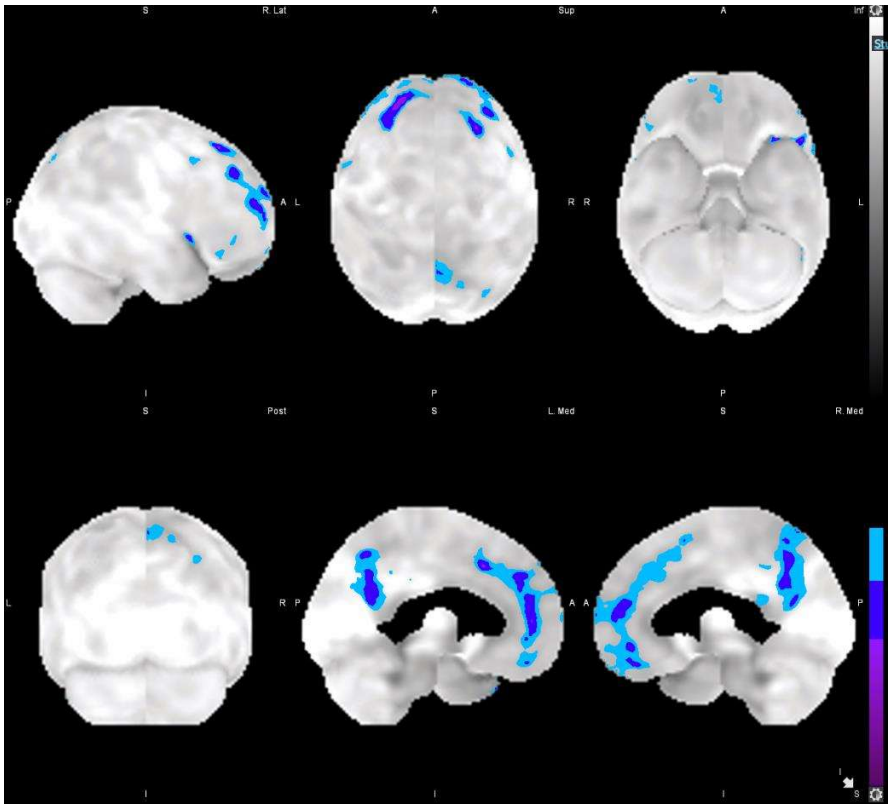

Figure 1. FDG-PET scan of the brain showing a mildly decreased metabolism in the frontal areas and precuneus.

Table 1 - Cognitive profile (RBANS) of the patient

RBANS	May 19th		June 17th		
	Total score	Z-score	Total score	Z-score	Interpretation
I. IMMEDIATE MEMORY	**61**	**-2,6**	**73**	**-1,8**	**Extremely low**
List Learning	17	-2,4	13	-3,3	Extremely low
Story Memory	10	-2,4	15	-1,0	Borderline
II. VISUOSPAT/CONSTRUCT	**58**	**-2,8**	**78**	**-1,5**	**Low**
Figure Copy	8	-5,9	15	-1,8	Low
Judgment of Line Orientation	9	-2,6	15	-0,6	Average
III. LANGUAGE	**78**	**-1,5**	**92**	**-0,5**	**Average**
Picture Naming	10	0,6	10	0,6	Average
Semantic Fluency	7	-3,0	17	-0,9	Borderline
IV. ATTENTION	**60**	**-2,7**	**68**	**-2,1**	**Extremely low**
Digit Span	6	-2,0	8	-1,0	Borderline
Coding	8	-4,8	22	-3,1	Extremely low
V. DELAYED MEMORY	**40**	**-4,0**	**75**	**-1,7**	**Low**
List Recall	0	-2,7	2	-1,8	Low
Story Recall	0	-4,4	7	-1,1	Low average
Figure Recall	0	-3,4	6	-1,9	Low
List Recognition	12	-6,2	18	-1,2	Low average

Online Resource 1 - Additional investigations in blood and cerebrospinal fluid

Laboratory Analysis
- **Blood Cell Analysis**: Sedimentation, Hematocrit, Hemoglobin, Erythrocytes, Mean Platelet Volume, Mean Corpuscular Volume, Leukocytes, Leukocyte Differentiation, Platelet Count, Mean Platelet Volume - **Biochemistry**: Urea, Creatinine, Glucose, Sodium, Potassium, Bicarbonate, Calcium, Phosphor, Magnesium, Ammonia, SGOT, SGPT, y-GT, Alkaline Phosphatase, Total Bilirubin, Conjugated and Unconjugated Bilirubin, Amylase, Lipase, Creatine kinase, CRP (C-Reactive Protein), Hba1c, Total protein, Protein Electrophoresis - **Endocrine and Vitamines**: TSH, T4, PTH, Vitamin B12, Vitamin D, Folic Acid, ANA, ANCA - **Infectious**: Blood cultures, Hepatitis B, HIV, Syphilis, Borrelia IgG, CMV (Cytomegalovirus) IgG & IgM, EBV (Epstein-Barr Virus) IgG & IgM, PCR Covid-19 - **Autoimmune:** Anti-NMDA, AMPA1/AMPA2, DPPX, GABAb, LGI1, CASPR2 Antibodies - **Drug monitoring**: Tacrolimus Whole Blood Level
Cerebrospinal Fluid Analysis (not all tests were repeated with each lumbar puncture)
- **Basic testing**: Leukocytes, Erythrocytes, Gram stain, (An) Aerobic Culture, Protein, Glucose, Lactate, Isoelectric Focusing, IgG - **Antibody testing**: Amphiphysin, CV2/CRMP5, Ma2, Yo, Hu, Ri, Recoverin, Sox1, Titin, Zic4, GAD65, NMDA, AMPA1/AMPA2, Gabab, Caspr2, LGI1, DPPX Antibodies - **Infectious**: Cryptococcus Antigen, Mycobacterium Tuberculosis, Polyomavirus, Enterovirus, Adenovirus, Herpes Simplex Virus-1 and 2, Human Herpesvirus 6, Varicella Zoster Virus, CMV, EBV, Toxoplasmosis, Borrelia - **Biomarkers**: T-Tau, P-Tau, Beta-Amyloïd, amyloid-$\beta_{1\text{-}42/1\text{-}40}$ ratio - Anatomopathology, Flow Cytometry

Online Resource 2 - Medication list at the time of admission and discharge from the neurorehabilitation clinic

At admission	At discharge
- **Tacrolimus Retard (Advagraf®):** 13mg o.d. - **Methylprednisolone:** 4mg, 2 tablets o.d. - **Pantoprazole:** 40mg o.d. - **Cetirizine**: 10mg o.d. - **Sodium bicarbonate**: 1g b.i.d. - **Magnesium**: 450mg o.d. - **Folic acid**: 4mg o.d. - **Calcium – Vitamin D**: 1000/880UI o.d. - **Lactulose (10g/15ml):** 10ml o.d. - **Tramadol Retard**: 100mg o.d. - **Tramadol Retard**: 50mg b.i.d. - **Tramadol**: 50mg b.i.d. - **Olanzapine**: 10mg b.i.d.	- **Cyclosporine**: 100mg b.i.d. - **Methylprednisolone**: 4mg, 1,5 tablet o.d. - **Sulfamethoxazole Trimethoprim 160/800mg**: 0,5 tablet, 2x/week - **Amitriptyline**: 10mg o.d. - **Haloperidol drops (2mg/ml):** 5 drops b.i.d. - **Pantoprazole**: 40mg o.d. - **Cetirizine**: 10mg o.d. - **Sodium bicarbonate**: 1g b.i.d. - **Magnesium**: 450mg o.d. - **Folic acid**: 4mg o.d. - **Calcium – Vitamin D**: 1000/880UI o.d. - **Lactulose (10g/15ml):** 10ml o.d. - **Topical Lidocaine 2,5 % + Prilocaine 2,5 % cream:** as needed, max 3 times per day - **Paracetamol**: 1gr, as needed, max 4 times per day

Abbreviations: o.d. once daily. B.i.d. bis in die, twice daily.

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