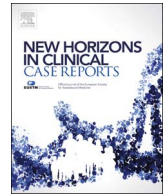




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The chemo brain: Severe cognitive decline following chemotherapy of breast cancer[☆]



Wolfgang P. Kaschka^{a,*}, Jürgen Steyer^b, Iris N. Kaschka^c, Martin Jandl^d, Steve Hodgkinson^a

^a University of Ulm, Department of Psychiatry and Psychotherapy I, Zentrum für Psychiatrie (ZfP) Südwürttemberg, Ravensburg, Germany

^b Zentrum für Psychiatrie (ZfP) Südwürttemberg, Ravensburg, Germany

^c University of Erlangen-Nuremberg, Department of Neuroradiology, Erlangen, Germany

^d University Hospital of Psychiatry, University of Bern, Switzerland

Introduction

Chemotherapy for different types of cancer is often life-saving. However, the spectrum of side effects may involve the central nervous system (CNS) and lead to severe emotional and cognitive disturbances, a syndrome often referred to as “chemobrain”. It is reported to occur with various degrees of severity in about two thirds of patients following chemotherapy [1,14,2,9]. At present, the mechanisms and determining factors of this syndrome are not well understood.

Case presentation

A 43-year-old female Caucasian patient was referred to our clinic as she had complained of frequent mood swings, found it difficult to concentrate and to remember what she had been told or read shortly before. Remarkably, in one instance she had left her electric iron switched on for several days and in another she had put a burning candle into a drawer and closed it afterwards.

Her medical history revealed that four years earlier breast cancer of the right breast had been diagnosed, and the patient had been tested positive for BRCA1 oncogen. At that time she had become a patient of a nearby Comprehensive Cancer Center (CCCU) and underwent breast-conserving therapy starting with systemic chemotherapy according to the GeparQuinto protocol (4xEpirubicin/Cyclophosphamide and 4xDocetaxel/Trastuzumab, 2×4 cycles; Trastuzumab for 1 year), additionally Goserelin. Six months after starting chemotherapy a breast-conserving operation was performed including axillary lympho-nodectomy. Tumor staging was as follows: ypT2, ypN1a (1/23), M0, L1, V0, R0, G3, ERO, PgR0, HER-2 status 3+. Surgery was followed by radiation therapy of the breast including the infra- and supraclavicular draining lymphatic systems applying a total dose of 66,4 Gy. At that time the patient found out that her mother and sister had also suffered from BRCA1-positive mammary carcinoma. She reported no mental health problems prior to her cancer diagnosis.

Convalescence of the patient proved to be protracted, and she

continued complaining of concentration and memory problems accompanied by mood swings and rumination. Four years after initial diagnosis she was admitted to our psychiatric inpatient department. She had been unable to work in her former profession as a manager of a car rental company due to her cognitive deficits. In addition, the long-lasting relationship with her boyfriend and business partner had ended. However, she had been able to begin a new relationship with a very empathic and supportive young man.

On admission, she was alert, fully oriented, but logorrhoeic, somewhat agitated, and showed depressed mood (Beck Depression Inventory, BDI, 48). There were no psychotic symptoms, and the patient denied having suicidal intents, but admitted having had suicidal thoughts previously.

On clinical examination, somatic including neurological findings were unremarkable, except for a slight, postoperative breast asymmetry (right < left).

On clinical grounds, the following differential diagnoses were considered: 1. Major Depression, 2. Bipolar II Disorder, 3. Epilepsy, 4. Frontotemporal Dementia, 5. HIV Encephalopathy, 6. Chemobrain.

Routine blood tests, HIV testing, ECG, routine and long-term EEG were all normal. CSF analysis: Total protein, albumin, IgG within normal ranges. Reiber diagram: No disturbances of the blood-brain-barrier (BBB), no intrathecal IgG synthesis; NMDA receptor antibodies negative, τ -protein and β -amyloid_(1–42) within normal ranges.

Cranial MRI (cMRI) including gadolinium enhancement was performed twice in this patient with a time interval of 28 months. The second examination (Fig. 1a,b) took place in our clinic and showed moderate brain atrophy with fronto-temporal accentuation (Fig. 1a). As a supplementary finding, an arachnoid cyst was detected at the left temporal pole (Fig. 1b). No metastases were found. In the earlier cMRI performed in a private radiology practice, slightly accentuated perivascular spaces, but no noticeable brain atrophy had been described. An arachnoid cyst (type I) of identical size and location had already been visible. Gadolinium enhancement had not been indicative of any further pathology.

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* Corresponding author.

E-mail address: wolfgang.kaschka@zfp-zentrum.de (W.P. Kaschka).



Fig. 1. a: cMRI, coronal section, T1 weighted, showing enlarged outer CSF spaces with fronto-temporal accentuation and normal width of the ventricles (Courtesy by Dr. Hinrich Prüß, Radiology Ravensburg). b: cMRI, horizontal section, T2 weighted, showing an arachnoid cyst at the left temporal pole (Courtesy by Dr. Hinrich Prüß, Radiology Ravensburg).

Extensive neuropsychological testing included components of the Wechsler Adult Intelligence Scale (WAIS), the Ray Auditory Verbal Learning Test (RAVLT), the Multiple Choice Vocabulary (“Mehrfachwahl-Wortschatztest”, MWT), the Regensburg Word Fluency Test (“Regensburger Wortflüssigkeitstest”, RWT), and the Test Battery for the Assessment of Attention (“Testbatterie zur Aufmerksamkeitsprüfung”, TAP). **Table 1** provides a short overview of the test results which reveal distinct impairment of several cognitive functions. Remarkably, the more verbally oriented tests which are known to be relatively resistant against organic brain damage showed normal results. Also, the MWT, which allows an estimation of the premorbid intelligence level, gave a result in the average range.

Considering the available data, we concluded that the most probable diagnosis in this patient was “chemobrain”. In the absence of evidence-based treatment recommendations for this syndrome, the

Table 1
Neuropsychological test results of the patient (for abbreviations see text; wherever possible, results are presented as $\bar{x} \pm S.D.$).

Tests performed	Results
MWT	IQ between 91 and 109, raw value: 21 points (average range: 85–115 points)
RAVLT	total learning: percent rank (PR): 75; T value: 56 delayed recall: PR 50–65; T: 50–53 loss after delay: PR 45–65; T: 48–54 corrected recognition: T: 53 (average range)
WAIS subtests:	
a) Number reproduction	9 points (within normal range)
b) Matrix test	6 points (distinctly below average)
RWT subtests:	
a) Lexical category: words beginning with K	PR 3%
b) Lexical category: words beginning with G-R	PR 2%
c) Semantic category: food	PR 8%
d) Semantic category: clothing - flower	PR 2%
	(all subtests far below average)
TAP subtests:	
a) Alertness	reaction time to visual stimulus <u>without</u> acoustic signal: $\bar{x} = 642$ (T=21) ± 162 (T=27) ms reaction time to visual stimulus <u>with</u> acoustic signal: $\bar{x} = 659$ (T < 20) ± 184 (T=24) ms (both far below average)
b) Flexibility	mean reaction time: 997 ms; T < 20 (far below average)
c) Go/No go	1 mistake (T=52) (average) mean reaction time: 558 ms; T=31 (far below average)

patient received antidepressive combination treatment with venlafaxin (112,5 mg/d) and mirtazapin (15 mg/d), supplemented by lithium carbonate (675 mg/d) and - because of her agitation and thought disorder (rumination) - neuroleptic treatment with aripiprazol (5 mg/d) and quetiapin (150 mg/d) under therapeutic drug monitoring (TDM). As an additional therapeutic measure, cognitive behavioral psychotherapy (CBT) was initiated. At discharge, the patient’s depressive symptoms had somewhat improved (BDI 36), but her status was otherwise unchanged. She has been lost to follow-up.

Discussion and conclusions

This case raises a number of issues, e.g. what are the causative and determining factors of chemobrain with regard to type of chemotherapy, dosage and combination treatments, such as cytostatic plus immunomodulatory agents? What are the respective roles and possible interactions of chemotherapy and radiotherapy in the pathogenesis of this syndrome? Experimental as well as clinical studies indicate that

CNS progenitor cells, neurogenesis, and oligodendrocytes are targets of chemotherapeutic agents [3], and that the resulting damage may be involved in the pathogenesis of chemobrain [4]. In a review of 53 studies, Wefel and Schagen [14] were able to identify a number of risk factors for chemotherapy-associated cognitive disturbances. The most prominent of them were: High total dose of chemotherapeutic agent, combinations of different substances, intraarterial or intrathecal application, additional radiation or hormonal therapy. The extent of loss of cognitive ability appears to depend, at least in part, on “cognitive reserve”, which in turn is dependent on age and educational level of the patient [10]. Interestingly, cognitive factors have been demonstrated to be associated with treatment adherence [11].

The fact that psychiatric examination and neuropsychological testing had not been performed before starting chemotherapy (and radiotherapy) in our patient constitutes a clear limitation of this case study.

With regard to therapeutic options, there is as yet no approved psychopharmacological treatment for chemobrain in Germany. Nevertheless, a number of substances have been investigated in this respect, and there is some evidence that off-label use of antidepressants and lithium (among others) may be helpful [2]. In addition, CBT has been shown to be superior to a control condition [7].

Another important question emerges from the follow-up cMRI findings in our patient. In the second cMRI, fronto-temporally accentuated brain atrophy was described, but no such finding had been visible in the first cMRI. Therefore, it could be asked, if progressive brain atrophy might be a constituent of the chemobrain syndrome in this case. Our observations support the notion that the use of more aggressive and combined treatment modalities in cancer therapy may cause delayed neuropsychiatric complications, such as cognitive decline, progressive myelin disruption, and brain atrophy [12,13,5,8].

Taking into account the high incidence of chemobrain (about two thirds of patients according to [9]) and its potentially deleterious impact on quality of life [2], it appears to be an important ethical issue whether information on the risk of developing this syndrome should be included in the informed consent obtained before starting these invasive treatments.

In terms of prevention, personalized chemotherapy for breast cancer and possibly other types of cancer should be envisaged as a long-term goal, regarding not only response behavior, but also tolerability, as has recently been suggested for radiation therapy [6].

Consent

Written informed consent was obtained from the patient for

publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

W.P.K. has received speaker's honoraria from Lundbeck GmbH, Hamburg. The other co-authors report no conflicts of interest.

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