

REVIEWS

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Brain MRI Findings in Neurological Complications of Cancer Treatment

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

The amount of people living with cancer is increasing; they live longer and have thus a higher risk of developing neurological complications. Magnetic resonance as a diagnostic procedure of choice in detecting the reasons of neurological/psychiatric symptoms in oncological patients is nowadays relatively easily accessible. Early diagnosis established by radiologists familiar with neurological entities that may follow cancer treatment allow clinicians to provide proper treatment, even if the diagnosis seems unbelievable. The review of MR images of acute and chronic neurological complications of cancer treatment from the authors' own archive is the focus of this report. Neurological complications of cancer can be metastatic and non-metastatic; the first cannot be considered as a treatment complication, the latter can be chemo- or radiotherapy-induced, acute, chronic and delayed. In our material we dealt with complications with dramatic course (stroke, PRES, acute leukoencephalopathy, Wernicke's encephalopathy) and with cases with milder and/or longer course (neuro-infections, chronic leukoencephalopathy, telangiectasias and/or cavernous hemangiomas, second tumors: glioma and meningioma after irradiation). The central nervous system is very susceptible to complications of systemic cancer and its treatment. Even though the first thought of clinicians and radiologists after a patient's first neurological/psychiatric symptoms appears concerns the metastatic spread of the disease, they need to have an understanding that there are a number of other causes of such symptoms. The knowledge of entities which can be expected and diagnostic experience prevent clinicians from making wrong diagnosis (*Adv Clin Exp Med* 2016, 25, 4, 789–797).

Key words: complications, brain, cancer therapy, magnetic resonance imaging (MRI).

The amount of people living with a diagnosis of cancer is increasing worldwide. Oncological patients live longer, thus laying themselves open to a higher risk of developing neurological complications. Magnetic resonance, as a diagnostic procedure of choice in detecting the reasons of neurological or psychiatric symptoms in oncological patients, is nowadays relatively easily accessible. Early diagnosis made by a radiologist familiar with the neurological entities that may follow cancer treatment allow clinicians to provide proper treatment, even if the diagnosis seems unbelievable to them, as it was in our patient with chondrosarcoma of the pelvis and femur and Wernicke's encephalopathy developed after only 6 days of parenteral feeding.

The purpose of this paper is to review magnetic resonance (MR) images of acute and chronic neurological complications in cancer treatment on the basis of the authors' personal experience and material including mainly, but not only, children treated for bone and soft tissue tumors and leukemia.

Discussion

Central nervous system complications of cancer can be:

- 1) metastatic,
- 2) non-metastatic:
 - radiotherapy-induced,

- chemotherapy-induced,
- side effects of surgical treatment of cancer,
- vascular disorders:
 - hemorrhage,
 - infarcts,
- metabolic and nutritional disorders,
- paraneoplastic syndromes,
- infections.

Metastases

Brain metastases cannot be treated as treatment complications; still they are the most common neurologic complication related to systemic cancer. They tend to be located at the gray-white junction and at anatomical “watershed” areas [1]. One has also to remember about the possible meningeal spread of metastatic lesions. The most common sources of brain metastases are lung, breast, kidney, skin and colorectal cancers.

Magnetic resonance imaging is a diagnostic procedure which can differentiate metastases from other lesions (like abscesses, primary brain tumors, demyelinating lesions, or inflammation). As compared to primary tumors, metastases are usually spherical and have more regular borders. Small lesions usually uniformly enhance with a contrast medium while larger ones tend to show ring enhancement. The tumor is usually surrounded by substantial edema. More or less one-half of brain metastatic lesions are single ones [2].

Non-metastatic Lesions As a Complication of Cancer Treatment

There is a wide spectrum of non-metastatic entities. Some neurological complications of cancer can be the result of the presence of primary disease itself. The other complications can be attributed to cancer treatment.

Radiotherapy-induced Complications

Radiotherapy-induced complications can be divided into acute, early delayed and delayed [2].

Acute reactions are rare, they occur within hours after radiotherapy (RT). Clinical symptoms include deterioration of previously existing deficits, headache, nausea and vomiting as a result of cerebral edema and are usually transient. Typically no pathological changes are observed on MRI.

Early delayed reactions like malaise, deterioration of the existing signs, seizures or somnolence occur weeks to a few months after radiotherapy and

they resolve over days to weeks. Usually MRI does not show the changes as in acute reactions [3]. Sometimes, T2-hyperintense area and contrast enhancement pattern not seen previously may be detected.

Delayed reactions can occur from 6 months to even many years after irradiation. Long-term survival of oncological patients is no longer a rarity; therefore radiologists are increasingly faced with the problem of recognizing these long-term complications. Delayed reactions include radionecrosis, leukoencephalopathy, secondary tumors and vascular disorders.

Radionecrosis has become less common over the past decades as a result of more neuroprotective protocols of irradiation. However, depending on the total dose, daily fractions and individual sensitivity radionecrosis has to be taken into consideration while making a diagnosis. Conventional MRI cannot distinguish radionecrosis from recurrent tumors. Metabolic imaging techniques (such as PET or SPECT), magnetic resonance spectroscopy and perfusion-weighted imaging can help to discriminate radionecrosis from a recurrent tumor [3].

Leukoencephalopathy, also called “diffuse radiation injury” or “radiation-induced leukoencephalopathy”, is becoming the most frequent complication in long-term survivors [4, 5]. MRI demonstrates diffuse T2-hyperintensity of the cerebral and cerebellar white matter (Fig. 1). It may be accompanied by ventricular dilatation and usually cortical atrophy (Fig. 2) [3].

Secondary tumors are a very late form of complication and occur 10–40 years after irradiation; the younger the radiated patient, the sooner we can expect a secondary tumor. The most common secondary tumors are: Meningioma (Fig. 3), sarcoma and malignant glioma (Fig. 4b). The risk of developing a second brain tumor in irradiated patients

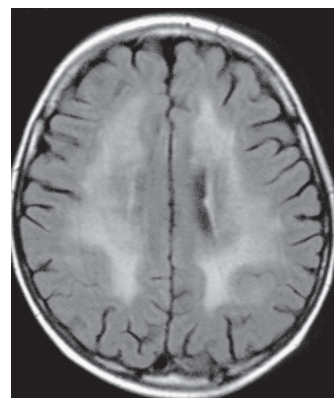


Fig. 1. A 10-year-old boy with leukoencephalopathy after irradiation due to acute lymphoblastic leukemia (ALL)

FLAIR, ax

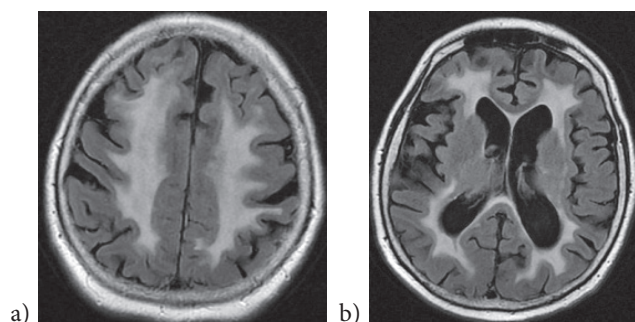


Fig. 2. Long-term survivor irradiated due to renal cancer. MRI demonstrates leukoencephalopathy accompanied by ventricular dilatation and cortical atrophy FLAIR, ax (a, b)

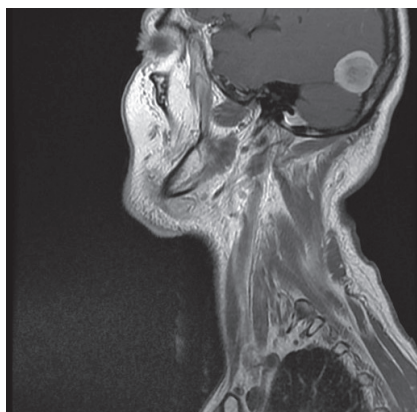


Fig. 3. Tentorium-related meningioma in a patient irradiated due to lingual cancer. SE/T1WI, sag after gadolinium administration

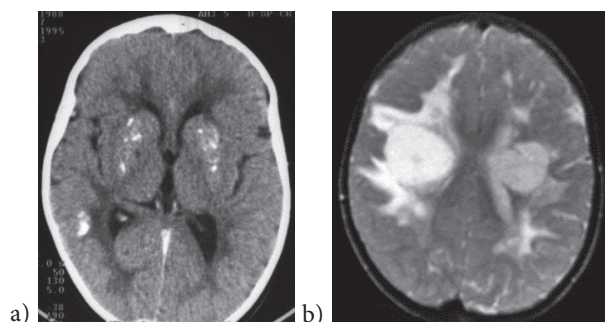


Fig. 4. A 7-year-old girl with ALL after irradiation. Necrotic leukoencephalopathy with calcifications (seen mostly in the basal ganglia) and a cavity in the right lentiform nucleus (CT – a). Four years later, at the age of 11, there is already a big cavity on the right and a secondary glioma in the deep structures of the left cerebral hemisphere (MRI, SE/T2, ax – b)

is 7-fold increased relative to the general population [6–8].

Vascular disorders generally follow radiation therapy by many years. Stroke is a result of radiation-induced occlusion of large or branch vessels. Arteriography reveals stenosis or occlusion of the artery within the radiation portal, sometimes asso-



Fig. 5. A 14-year-old boy who developed cavernous malformation in the brain stem 4 years after radiation treatment for ALL

SE/T2WI, ax

ciated with moyamoya disease. Radiation may also induce capillary telangiectasias which develop approximately 3–9 months after RT and cavernous malformations which develop later: 3–9 years after RT [9]. They display low signal intensity on T2- and T2*-weighted images (Fig. 5). Such foci may also represent calcifications, but these occur mainly in the basal ganglia (Fig. 4a).

Chemotherapy-induced Complications

Neurotoxicity of antineoplastic drugs is frequent and – like in the case of radiation-induced complications – dose-dependent. Chemotherapy-induced complications have a wide spectrum of clinical manifestations including posterior reversible encephalopathy syndrome (PRES) (Fig. 6.1), acute encephalopathy (Fig. 7), stroke-like episodes, chronic encephalopathy (Fig. 8), intracranial hemorrhage (Fig. 9) or cerebellar syndrome. Chemotherapeutic drugs which are responsible for the majority of cases of encephalopathy are methotrexate, vincristine, ifosfamide, cyclosporine, fludarabine, cytarabine, 5-fluorouracil, cisplatin and interferons [10].

PRES is an increasingly recognized complication of cancer treatment because of increased intensity of chemotherapy and because of easier access to magnetic resonance imaging. PRES is manifested most commonly by seizures. Headache, altered mental status and visual impairment also belong to the clinical picture of this entity. PRES is a consequence of increased blood pressure, endothelial dysfunction with subsequent blood-brain barrier damage and of the subsequent cerebral vasogenic edema. Both hypertension and higher seizure susceptibility of the brain may be caused by cytotoxic effects of anti-cancer drugs [11, 12].

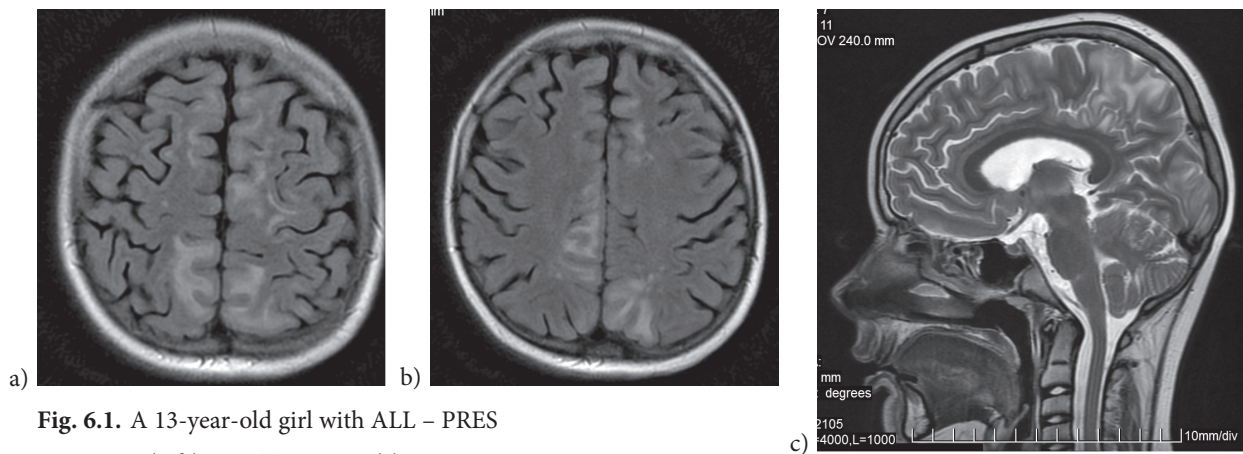


Fig. 6.1. A 13-year-old girl with ALL – PRES

FLAIR, ax (a, b), FSE/T2WI, sag (c)

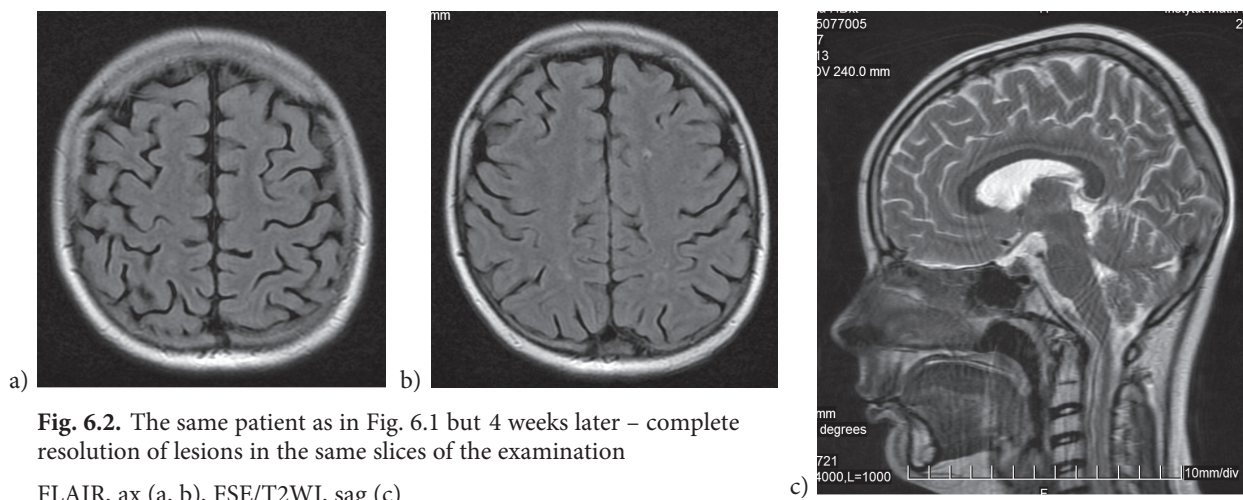


Fig. 6.2. The same patient as in Fig. 6.1 but 4 weeks later – complete resolution of lesions in the same slices of the examination

FLAIR, ax (a, b), FSE/T2WI, sag (c)

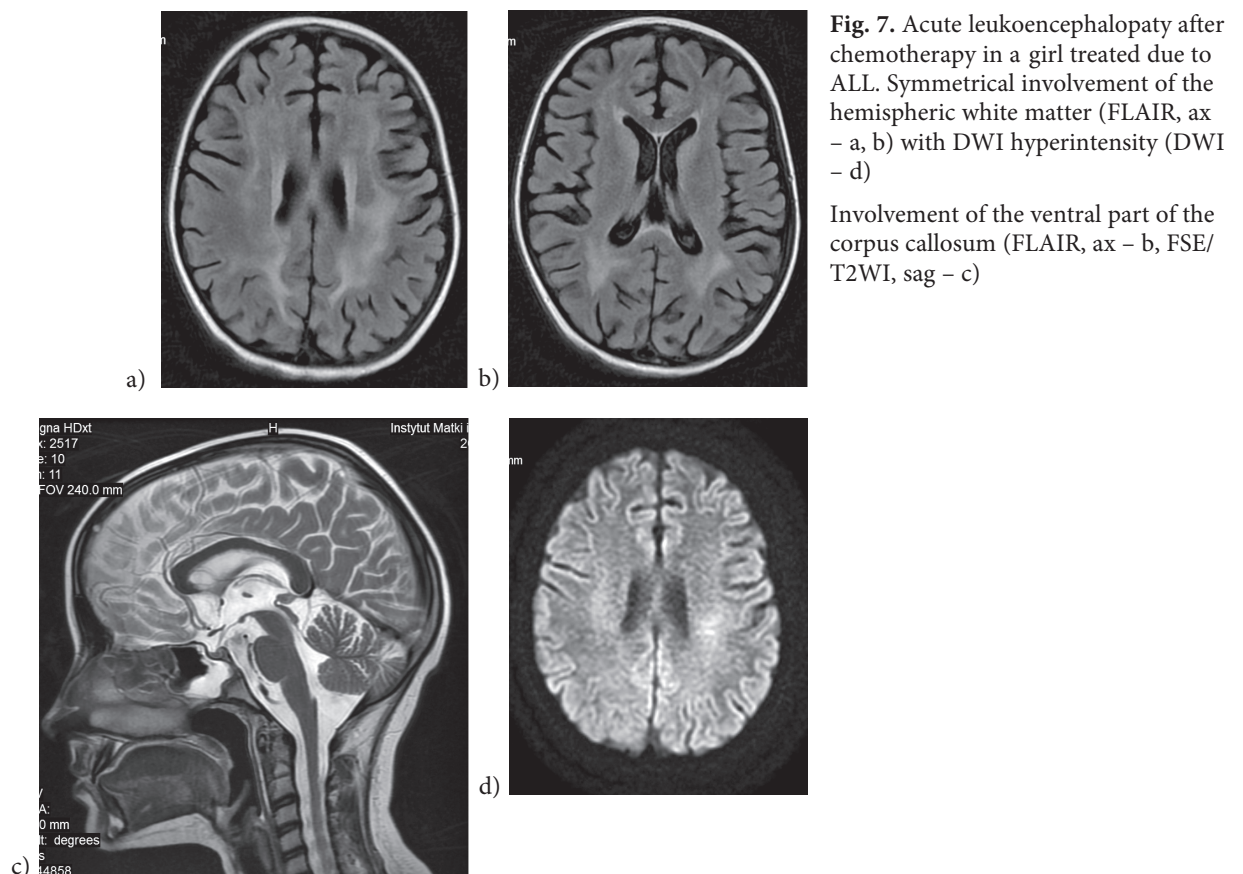


Fig. 7. Acute leukoencephalopathy after chemotherapy in a girl treated due to ALL. Symmetrical involvement of the hemispheric white matter (FLAIR, ax – a, b) with DWI hyperintensity (DWI – d)

Involvement of the ventral part of the corpus callosum (FLAIR, ax – b, FSE/T2WI, sag – c)

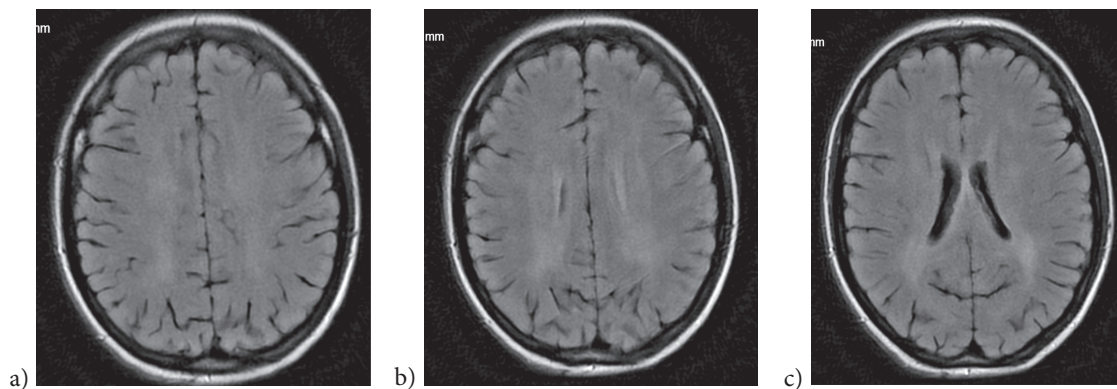


Fig. 8.1. Leukoencephalopathy in a girl receiving chemotherapy due to osteosarcoma of the cranial vault FLAIR, ax (a, b, c)

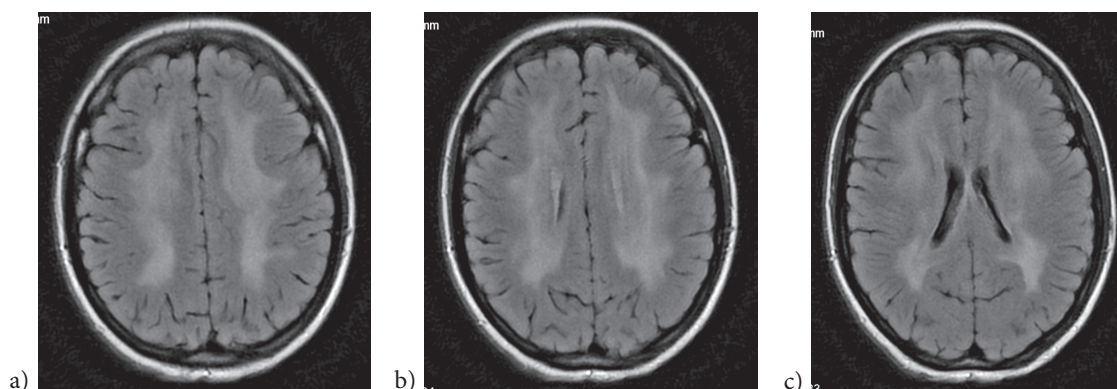


Fig. 8.2. The same patient as in Fig. 8.1 but 9 months later – chronic leukoencephalopathy FLAIR, ax (a, b, c)

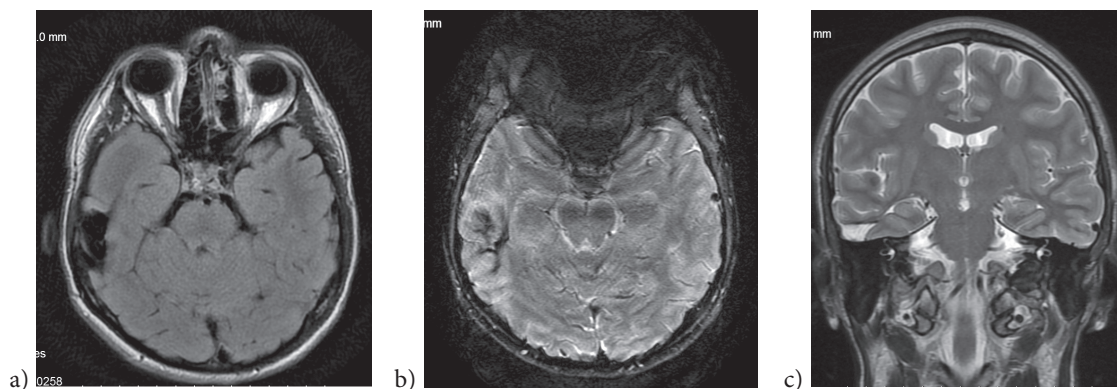


Fig. 9. An 18-year-old boy 15 years after treatment due to ALL. Chemotherapy was then complicated by intracerebral hemorrhage in the right temporal lobe. MRI shows a posthemorrhagic scar with hemosiderin deposits. Note the artifacts in SWI sequence caused by braces. FLAIR, ax – a; SWI; ax – b; FSE/T2WI; cor – c

Typical, transient lesions of PRES are T2-hyperintense and localized in the subcortical white matter (Fig. 6.1). The abnormalities occur predominantly in the posterior temporal, parietal and occipital areas. Moreover, PRES may affect the basal ganglia, cerebellar hemispheres and the brainstem. In about 90% of cases symptoms and radiological findings normalize (Fig. 6.2). In 10% of cases MRI shows persistent abnormalities [11].

The diagnosis of chemotherapy-induced complications can be usually made based on conventional MR images. In some cases, a diagnosis of acute leukoencephalopathy can be made only based on diffusion-weighted imaging which reveals high signal intensity in the deep white matter of both cerebral hemispheres, including the corpus callosum, while standard sequences remain silent [13].

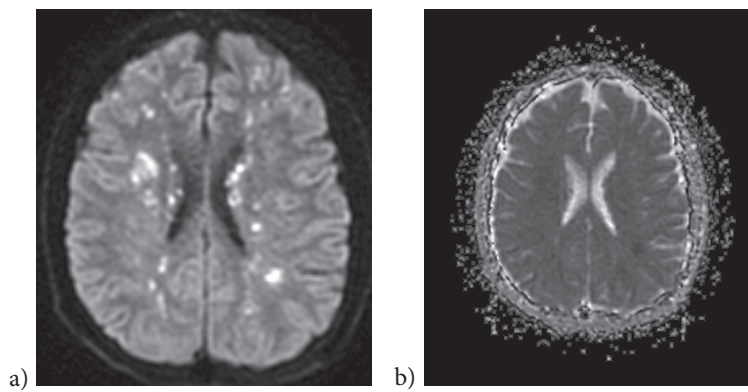


Fig. 10. A 17-old boy after resection of proximal part of femur due to bone tumor and endoprosthesis implantation

Acute neurological deterioration immediately after the operation was most likely due to fat or air emboli which resulted in multiple, tiny acute infarcts disseminated in the whole brain. DWI, ax – a, ADC, ax – b

Side Effects of Surgical Treatment of Cancer

Surgery due to neoplasms carries the same risk as that due to other diseases and include: Damage to the other organs in the body, adverse reactions to medication, blood loss and, sometimes, air or fat embolism (Fig. 10).

Vascular Disorders

Hemorrhage

Cerebral hemorrhage may be seen in patients with hemorrhagic metastases, in patients with leukemia, thrombocytopenia, or coagulopathy (Fig. 9).

Stroke

Cancer and its treatment often induce a hypercoagulable state; therefore, cerebral infarcts are often seen in oncological patients. Venous sinus thrombosis is another manifestation of hypercoagulability. There are also reports of embolic strokes from tumor cell embolization or the tumor's direct invasion of blood vessels [14, 15].

Venous sinus thrombosis may lead both to cerebral parenchymal infarcts and hemorrhages. It may occur, among others, because of the anti-cancer medication, L-asparaginase, which is used in the induction therapy of acute lymphocytic leukemia and predisposes to prothrombotic state [16].

Metabolic, Nutritional Disorders

Metabolic or nutritional abnormalities related to the underlying cancer may lead to diffuse encephalopathy. There is a variety of disorders which may result in metabolic or nutritional dysfunction, e.g. hypoxemia, fever, electrolyte imbalance, hyperammonemia, hepatic failure, metabolic acidosis, thiamine deficiency (Wernicke's encephalopathy) and many others.

Wernicke's encephalopathy (WE) may be caused by imbalanced or poor nutrition, chemotherapy-induced nausea and vomiting, con-

sumption of thiamine by rapidly growing tumors or prolonged total parenteral nutrition without the addition of thiamine. Clinical mental confusion is an initial manifestation, with rapid deterioration [12]. MRI findings include the symmetrical T2-hyperintensity of the medial thalami, mamillary bodies, tectal plate, periaqueductal area, and floor of the fourth ventricle (Fig. 11.1 b, c, d, e).

Atypical locations are: Nuclei of the cranial nerves, dentate nuclei, vermis, putamina, red nuclei, caudate nuclei, callosal splenium, and cerebral cortex [17]. These atypical locations have been more frequently described in nonalcoholic WE. Involvement of the cerebral cortex is rare and associated with a worse prognosis as potentially irreversible brain damage [11]. However, in our case, cortical lesions (Fig. 11.1 a) resolved completely (Fig. 11.2 a) and the patient's neurological and psychiatric status returned to normal.

Paraneoplastic Syndromes

Paraneoplastic neurological syndromes (PNS) are rare disorders appearing in patients with cancer but not caused by direct invasion, metastasis or by consequences of cancer treatment. They are usually autoimmune in nature. PNS can present with multiple clinical manifestations like paraneoplastic encephalomyelitis, limbic encephalitis, paraneoplastic cerebellar degeneration, autonomic failure, cerebellar ataxia, visual complaints and many others. MRI findings depend on the affected region of the brain and are usually associated with the abnormal T2 signal [18–20].

Infections

The suppressant effect of cancer and its treatment on the body's immune system can result in infectious complications within the nervous system. Immunocompromised patients are susceptible to bacterial (Fig. 12), fungal and viral infections (Fig. 13), especially caused by opportunistic agents. It has been shown that, for example,

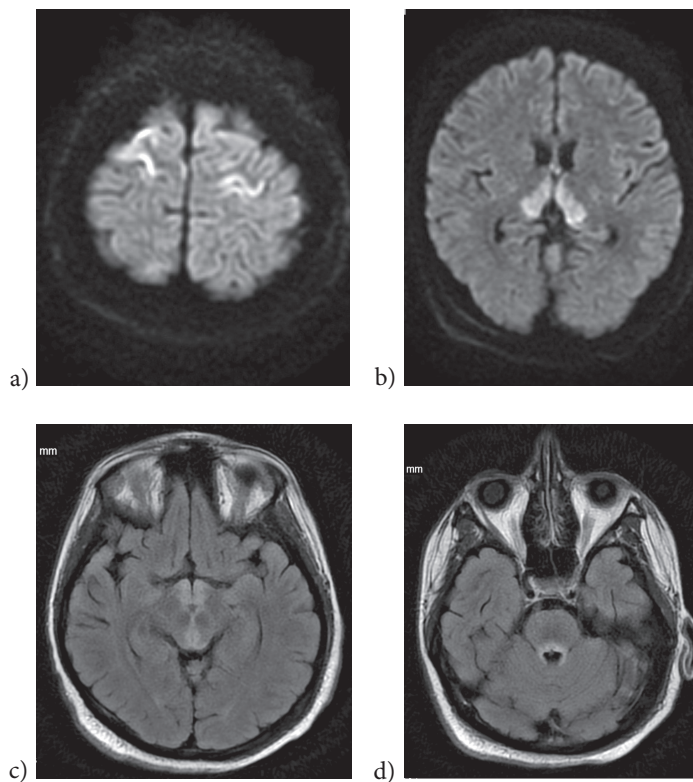


Fig. 11.1. Typical MRI pattern of Wernicke's encephalopathy in a 20 year-old patient after hemipelvectomy due to chondrosarcoma complicated by colorectal injury

After only 6 days of parenteral feeding his psychiatric and later neurological status deteriorated. DWI, ax – a, b, FLAIR, ax – c, d, e

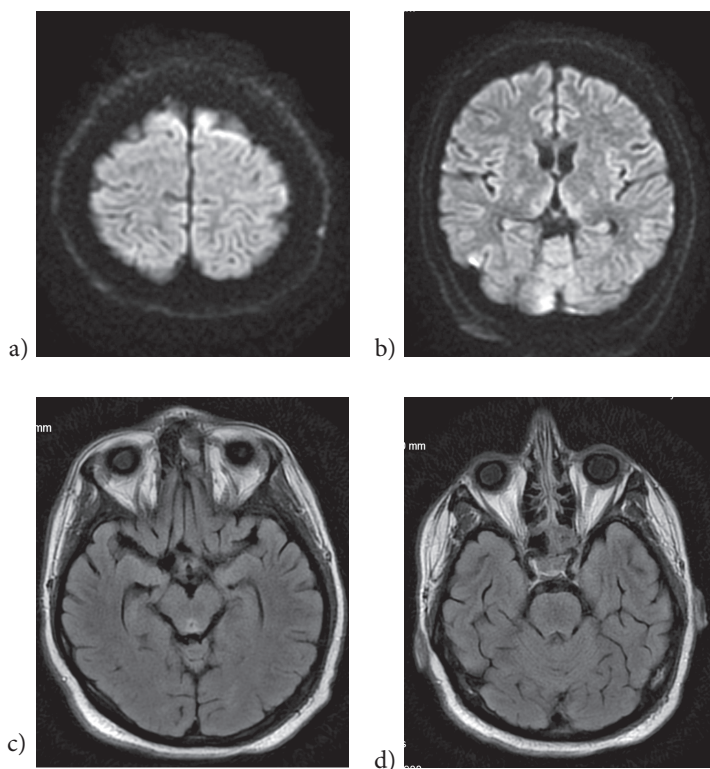


Fig. 11.2. Almost complete regression of the lesions after treatment with thiamine. MRI performed one month later – the same slices of the examination

DWI, ax – a, b, FLAIR, ax – c, d, e

human herpes virus is transmitted through bone marrow transplantation [16]. One should remember that symptoms of the disease in patients receiving chemotherapy or hematopoietic stem cell transplantation tend to be worse than in immunocompetent patients, but early diagnosis and prompt treatment often result in recovery.

Summary

The central nervous system is very susceptible to complications of systemic cancer and its treatment. Even though the first thought of the clinician and the radiologist after patient's first neurological or psychiatric symptoms appear concerns

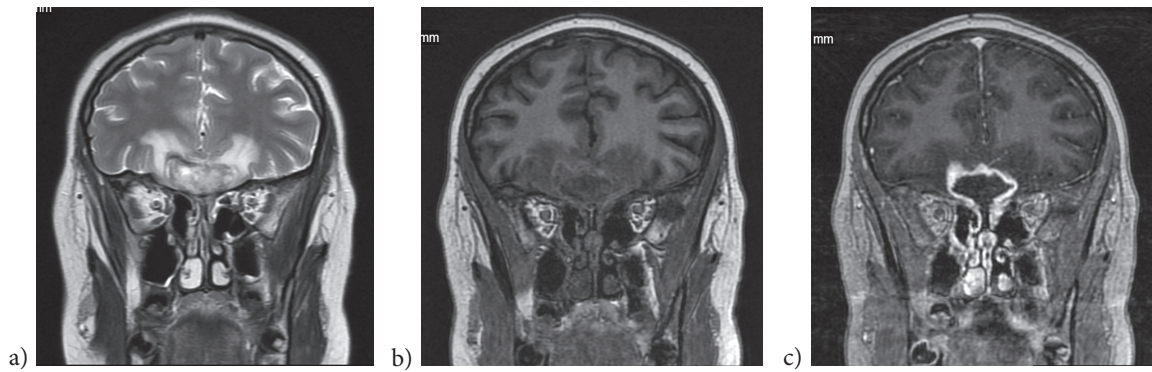


Fig. 12.1. A 16-year-old girl with rhabdomyosarcoma of the hand

The infiltration of the frontal lobes was considered as infectious and mixed bacterial infection (methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*) was confirmed. FSE/T2WI, cor (a), 3D/T1WI, cor before (b) and after (c) gadolinium injection

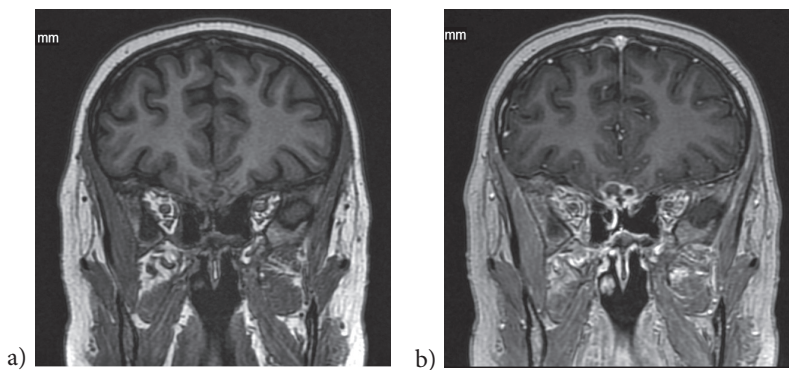


Fig. 12.2. After 4 months of antibiotic treatment (Vancomycin) the lesion is smaller. 3D/T1WI, cor before (b) and after (c) gadolinium injection

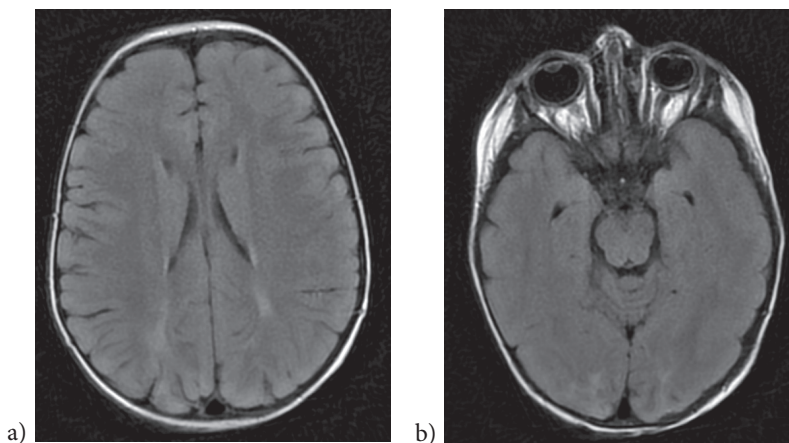


Fig. 13. This 3-year-old girl was treated due to neuroblastoma. She received bone marrow transplantation which was complicated with CMV infection. Post-inflammatory lesions are depicted by MRI. FLAIR, ax (a, b)

the metastatic spread of the disease, they need to have an understanding that there are a number of other causes of such symptoms. The knowledge of

entities which can be expected and diagnostic experience prevent from making a wrong diagnosis.

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