**Oncological emergencies: Increased intracranial pressure in solid tumours’ metastatic brain disease**

**Introduction**

Increased intracranial pressure due to metastatic brain disease is one of the oncological emergencies. It may cause herniation or insufficient brain blood flow, thus it is a life-threatening condition. This article focuses on diagnostic and treatment options, which should be introduced immediately. The prognosis remains poor.

**Etiology**

Among diverse causes of the increased ICP in oncological patients large brain metastases are the most common [1]. Table I presents the most frequent primary histology for metastatic brain cancer. Metastases may be complicated by intracranial hemorrhage (IH), usually intratumoural [2]. It is important to notice that IH is frequent in metastatic melanoma, lung and breast cancers [3]. However some malignancies: thyroid cancer, hepatocellular carcinoma, and choriocarcinoma- that rarely seed to the brain- have a special predisposition to provoke hemorrhage [2]. Coagulopathy, which is widely observed in oncological patients, is the second most common cause of IH [4]. Any compartment may be involved, but intraparenchymal hemorrhage (IPH) is the most common followed by subdural hemorrhage, subarachnoid hemorrhage and epidural hemorrhage [2]. It is not unusual to see many of them involved simultaneously, including ventricular system [2]. Metastatic brain tumour increases brain blood barrier (BBB) permeability creating vasogenic oedema through leaky capillaries with impaired endothelial tight junctions [5] and is the major cause of brain swelling in oncological patients [6]. Vasogenic oedema is also observed in bacterial abscess and cerebral hemorrhage [1]. Immunocompromised patients are more susceptible to infections of the nervous system in the form of meningitis, encephalitis or abscess which increase the ICP [1]. Cytotoxic oedema is induced by ischemic injury, cytotoxic chemotherapy agents, or toxic metabolites in liver failure [1]. Another group (1-5%) of patients suffers from hydrocephalic oedema caused by either obstructive or communicating hydrocephalus [7]. Physiological flow of constantly produced CSF may be blocked by mass localised close to foramen of Monro, cerebral aqueduct, medullary foramina or basal subarachnoid cisterns resulting in non-communicating hydrocephalus [1]. Increased intraventricular pressure causes CSF to migrate through the ependyma into the periventricular white matter with a rise of the extracellular fluid volume [8]. Osmotic oedema may occur in case of hypoosmolar conditions including syndrome of inappropriate anti-diuretic hormone secretion or improper administration of intravenous fluids, both leading to acute dilutional hyponatremia. Osmotic oedema arises also when the plasma osmolality is normal, but tissue osmolality is high in the core of the lesion as in the case of brain haemorrhage or infarct [8]. Venous outflow obstruction related to the tumour manifests primarily with increased ICP [9]. In solid tumours the cause is usually nonthrombotic: compression or invasion of the cerebral sinuses (predominantly sagittal) by metastatic lesions located in dura or calvaria [10].

**Pathophysiology**

Compensatory mechanism attenuating increase in the ICP relies on the reduction of the CSF compartment volume. CSF is initially forced from the cranial subarachnoid spaces and lateral ventricles into the spinal subarachnoid space [11]. The bigger the CSF volume and the slower the growth of additional mass in the brain, the more effective the compensatory mechanism. However normal CSF flow, production and
reabsorption as well as open dural venous sinuses are essential. Nevertheless with ICP over 200-250 mm any further volume increase is followed by disproportionate rise of pressure. The consequence may be impaired cerebral perfusion pressure (CPP = mean blood pressure – ICP), described as plateau waves when lasting over 5 minutes. Unless they last longer than 30-40 minutes the prognosis is not getting worse [12]. With ICP over 40-50 mm Hg cerebral blood flow becomes insufficient leading to permanent brain damage [1].

The immediate reason for herniation is the gradient in the intracranial compartmental pressure [13]. It causes parenchymal tissue shifts with impairment of different structures depending on location. Ischemia or infarction from vascular compression may cause oedema and further deterioration in compliance.

Symptoms
Severe headache is the most common complaint, in the beginning mainly at night and early in the morning, with a tendency to escalate. It is usually similar to tension-type, but may be getting worse with bending over [14]. Typical analgesics are not effective. Vomiting: often without nausea- brings relief and is frequently observed when the pain reaches its maximum intensity. Progressive character of pain strongly suggests oedema development [15]. Patients fall easily, especially backwards [1]. The state of consciousness is diminished and ranges from somnolence to coma. In funduscopic examination papilledema is observed in half of the patients; absence of venous pulsations within the centre of the optic disc is an early finding followed by blurring of the disc margins with small haemorrhages [1]. In the early stage vision acuity is preserved, but acute onsets of blindness and visual field decline may follow. Seizures are observed in 10-15% of patients, especially with haemorrhage into metastatic focus. Focal neurological deficits depend on the localisation of the mass that caused the increase of ICP. Classical Cushings triad: hypertension, bradycardia, and irregular respiration or apnoea is usually incomplete [16]. In meningial carcinomatosis classical signs of meningial irritation are rarely seen [1], nevertheless they are often present in patients with increased ICP. If the ICP is increased chronically patient may lose control over bladder sphincter.

As long as the ICP does not change dynamically little or no symptoms ensue. The patient’s state declines rapidly with herniation that is highly probable when there is a new, large intracranial volume. Uncal herniation: typically caused by temporal lobe masses- presents with an acute deterioration of consciousness with ipsilateral papillary dilatation and contralateral hemiparesis, with Babinski sign due to compression of the cerebral peduncle [1]. Progression of the brain shift is revealed by complete oculomotor (III) nerve palsy and stupor, as ascending arousal pathways are not working. Supratentorial mass may give rise to transtentorial (central) herniation. The symptoms reflect the progress of brainstem structures damage described as diencephalic, mesencephalic and pontine stages. The process starts with patient’s compromised arousal (inattentiveness) with breathing rhythm disturbance, yawning and hiccuping [16]. As the process continues the patient becomes obtunded or stuporous. Roving eye movements (slow, conjugate, lateral, to and fro excursions) may appear if third nerve nuclei and connections are intact while hemispheres are bilaterally dysfunctional. Patient adopts decorticate posture with bilateral flexion of the upper limbs and extension of the lower limbs in response to pain. Pupils are not responding to light. Failure of mesencephalic reticular activating system results in coma. Breathing is fast and remains regular. Decerebrate posture with all limbs extended to pain stimuli indicates pontine stage, confirmed by doll’s head manoeuvre (eyes do not move conjugately in the direction opposite to the head movement) and- if the latter is negative- caloric response (ice-cold water applied to the tympanic membrane normally elicits a slow conjugate deviation to the irrigated side). Pupils are dilated and fixed. Breathing becomes apneustic and finally stops and the blood pressure drops [1].

Diagnosis
The most important diagnostic tools are the history and clinical examination. With the initial presumption and the patient stabilised neuroimaging should be obtained. Cranial computed tomography (CT) is preferred over magnetic resonance imaging (MRI) due to availability and speed of imaging [16]. (Figure 1 presents a head CT with multiple metastatic lesions in both hemispheres). In the majority of cases unenhanced CT will identify the underlying process. In order to characterise the lesion MRI with intravenous gadolinium is particularly useful as the BBB is compromised so that distinction between a neoplastic, infectious, inflammatory or ischemic disease is more vivid. MRI is more sensitive and provides more detailed information about dural involvement [17]. MRI and MR venography can accurately diagnose cerebral sinus thrombosis in cancer patients [7]. Lumbar puncture allows CSF pressure measurement. Intracranial hypertension is defined as a sustained (>5 min) elevation of the ICP of >20 mmHg. However there are no indications for ICP monitoring in cancer patients [18]. Furthermore in traumatic brain injuries the ICP monitoring does not seem to be superior to care based on clinical examination and imaging [19]. Nevertheless lumbar puncture is a necessity in certain clinical situations like making an accurate diagnosis of cryptococcal meningitis [1]. Contraindication for lumbar puncture is compartmentalisation, revealed by CT scan. Compartmentalisation is a result of obstructive hydrocephalus or obliteration of basal cisterns due to herniation. Thus CT inevitably precedes while there is a serious risk of initiating or exacerbating the herniation. Transcranial Doppler ultrasonography is helpful in monitoring cerebral perfusion in patients with increased ICP [1].

Management
While increased intracranial pressure occurs as a heterogenous group of conditions, treatment of acute hypertension requires a thorough understanding of its pathophysiology.

I. Symptomatic treatment
Start with assessment for adequate circulation, airway patency, and ventilation. Patient’s head should be elevated to 30 degrees in order to facilitate cerebral venous drainage [3]. Hyperthermia is treated with antipyretics. Only iso- or hypotensive fluids should be used as intravenous solutions [16]. If hypotension is present steps should be initiated for correction. Serum osmolality should stay in the high normal range [1]. Blood pressure (BP) control in the context of increased ICP is quite unique . It should be focused on eliminating acute peaks and drops that could impair CPP. In order to reduce BP labetalol, esmolol and nicardipine are recommended, whereas phenylephrine, table 1

<table>
<thead>
<tr>
<th>Primary histology</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>15-64%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2-21%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>2-12%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4-16%</td>
</tr>
<tr>
<td>Kidney</td>
<td>1-8%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1-10%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1-18%</td>
</tr>
</tbody>
</table>

CT showing multiple melanoma metastatic lesions (the arrows) in both hemispheres of the brain localised supratentorially and infratentorially with associated oedema.

The mass effect is illustrated by the midline shift in the frontal region. There are no clear signs of herniation.

TK uwidacza liczne ogniska przerzutów czerwieni (strzałki) w obu płatkach mózgowych, są one zbadane zarówno nadnamiotowo jak i podnamiotowo, towarzyszą im obrzęk.

Efekt masy uwidacza się poprzez przeniesienie linii pośrodkowej w regionie płetw czołowych. Nie można doszczyć jednoznacznych objawów wglądania.
norepinephrine and dopamine can be used to raise BP [13].

In symptomatic patients corticosteroid therapy is initiated for vasogenic oedema resulting from brain tumours, abscesses or non-infectious neuroinflammatory conditions with a starting dose of 4–8 mg/day of dexamethasone. If patients exhibit severe symptoms higher doses such as 16 mg/day or more may be needed. Therapy withdrawal should take two weeks or longer in symptomatic patients [20]. Another option is to try to shrink the brain by dehydrating effect of serum hyperosmolality. The beneficial effect of hyperosmolar therapy requires effective BBB. Otherwise equilibration of molecules between blood and the interstitial fluid of the brain is undermining the treatment. Consequently hyperosmolality has a limited effect on brain oedema surrounding a mass lesion, but removes water rather from the healthy brain tissue [11]. Superiority of hypertonic saline (HTS) over mannitol is currently widely discussed also in this context [6,21]. Monitoring of serum osmolality is required with a target of 300 to 320 mOsmol/kg to prevent the clinical circumstances [11]. Only after the ICP drops the osmolality can be normalised, in order to prevent the rebound effect ensuing reverse of water gradient [11]. If HTS with a concentration of more than 3% is chosen a central venous catheter should be inserted [11]. In HTS treatment the serum Na level of around 150 mmol per litre is desired. It can be achieved either in bolus or continuous drip infusion with a wide range of concentrations: 2-23.4% [6,11,21]. 20% mannitol solution at initial doses of 0.25 g/kg to 1 g/kg body weight. It can be followed by lower doses every 3-6 hours [1]. Arterial hypotension (systolic blood pressure < 90 mm Hg) should be avoided [22]. The levels of serum sodium or serum osmolality, blood urea nitrogen and serum creatinine should be measured regularly [5]. The quickest method of decreasing ICP is intubation and a brief course (<2 h) of mechanical hyperventilation to a PCO2 of 30–35 mmHg [13]. Lower level could cause reduction in cerebral perfusion [1].

Obstructive hydrocephalus is a neurosurgical emergency. Signs and symptoms of progressive herniation force the immediate placement of external ventriculostomy [1]. In due course patients have different treatment options depending on their class in the recursive partitioning analysis (RPA) of prognostic factors [23]. Class I is defined by poor performance status (KPS) > 70, < 65 years of age, with controlled primary disease and no extracranial metastases; Class II consists of those with KPS < 70, while Class II includes all the others. Thus good surgical candidates, who belong to Class I according to RPA, may be treated with surgical resection of the offended lesion. Poor surgical candidates have been historically treated with ventriculoperitoneal shunting (VPS). However a subset of patients can benefit from endoscopic third ventriculostomy [7]. VPS carries the risk of peritoneal dissemination or accumulation of malignant ascites in patients with leptomeningeal metastasis [24].

II. Causal treatment

Whenever it is possible disease-specific treatment follows symptomatic management.

1. Surgery

Neurosurgical intervention is an aggressive form of treatment from which patients of I and II class of RPA are more likely to benefit [22]. Resection of a single brain metastases leads to improved overall survival, better quality of life and local control of the disease compared to whole brain radiation therapy (WBRT) alone [25]. The location of the lesion is important as thalamic, basal ganglia and brainstem metastases are not usually considered for resection [26]. Thus, unfortunately, only 15% of all the patients with brain metastases may undergo surgery [25]. Patients with multiple metastases may be candidates for surgery provided each lesion is considered resectable. If all lesions are not considered resectable, surgery may be considered for those symptomatic lesions that are resectable [26]. The value of adjuvant WBRT is questionable [25]. Another option is stereotactic radiosurgery (SRS) therapy, which is more tolerable by patients and allows managing of deep-seated lesions being good alternative to surgery, especially in case of small (≤3 up to 4 cm) metastases [25].

2. Radiotherapy

Radiotherapy (RT) is an important treatment modality in the management of cancer patients. However, there are few publications dealing with an urgent administration of RTH in patients with symptomatic increased ICP [27,28]. A questionnaire (for example the Edmonton Symptom Assessment System - ESAS) could be a first-line tool to measure the severity of symptoms and decide whether emergency treatment is needed. ESAS is an eight-grade visual analogue scale that combines the level of pain, activity, depression, anxiety, appetite, nausea, drowsiness and perception of well-being. The questionnaire is completed by the patient single-handedly, by the patient with the nurse’s assistance, by the nurse alone, or by the relatives. The final result is defined as the symptom distress score [29]. RTH schedules: 6 Gy administered twice daily up to a total dose of 12 Gy, repeated after 4 weeks in those who respond and total dose 30 Gy in 10 fractions give symptomatic relief in 64% and 63% of patients, respectively [28]. According to German data the median improvement rate was 70% [27]. Previous RTH does not disqualify patients from emergency irradiation and clinical practice suggestions where outlined for this particular cluster [32]. During RTH corticosteroids are strongly recommended in order to prevent side effects.

3. Chemotherapy

If only the patient’s condition allows, the systemic treatment (chemotherapy [CTH]) should be introduced. However we have not found any guidelines or data about control of the symptoms by CTH in this group of patients. Although its activity is not rapid, in certain groups of patients with better prognosis (RPA class I), CTH may be beneficial.

Prognosis

Except from the patients who undergo focal brain therapy, survival time in patients with symptomatic brain metastases is approximately 1 to 2 months without therapy, 2 to 3 months with corticosteroid therapy, and 3 to 6 months with WBRT [28].

Conclusion

As the prognosis is extremely poor it is a strong argument for eschewing from the most aggressive forms of therapy, especially in the patients from RPA class III [25]. The quality of patient’s life should be the main concern.

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