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Drug-Induced Encephalopathy

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1. Introduction

Drug-induced encephalopathy is a disease entity often caused by impaired cerebral metabolism that is not attributed to structural brain lesions. However, some drug-induced encephalopathies can develop structural lesions and share other underlying pathophysiological mechanisms (table 2). Leading symptoms are acute or chronic disturbances of consciousness, brain function and personality changes with concomitant neurological symptoms such as asterixis, myoclonias, paresis or seizures (see table 3). Isoniazid-induced encephalopathy was one of the earliest descriptions of a drug-induced encephalopathy (Adams & White, 1965). Clinical symptoms depend on the type and severity of the drug-evoked encephalopathy. A well-described and frequently-reported drug-induced encephalopathy is valproic acid encephalopathy, first described in the late 1970s. This acute encephalopathy was characterized by altered behaviour, worsening seizure control and confusion. After a reduction in the valproate acid dose, the patient's symptoms resolved completely (Chadwick et al., 1979). Encephalopathies have been reported after consumption of several types of drugs as depicted below (table 1).

2. Drugs

2.1 Analgesics and anaesthesia

Drug-induced encephalopathy was reported after morphine administered intrathecally and the use of propofol (Eran & Barak, 2009). Morphine has been described as having induced an encephalopathy characterized by a myoclonus, motor dysfunction, or vertigo (Goundrey, 1990; Kakinohana et al., 2003). Spinal anaesthesia with hyperbaric bupivacaine lead to an encephalopathy that developed a few days after the drug's administration (Ho & Chan, 2007). A drug abuse-evoked encephalopathy was also reported after ketamine and gamma hydroxybutyrate (Virmani et al., 2010). Toxic encephalopathy has been described after intake of an acetaminophen overdose (Brusilow & Cooper, 2011).

2.2 Antibiotics

Drug-induced encephalopathy can occur after an intake of cefepime and metronidazole (Kim et al., 2011; Lin et al., 2011). The incidence of metronidazole-induced encephalopathy is unknown. Several studies addressed reversible brain changes caused by metronidazole

induced-encephalopathy (Ahmed et al., 1995), and bilateral, symmetric brain abnormalities have been observed in patients (Ahmed et al., 1995; Kim et al., 2011). Ceftriaxone induced a reversible encephalopathy in an patient treated for a urinary tract infection (Rancon-Albuquerque et al., 2009). That encephalopathy was completely reversible. An early-onset encephalopathy a day and a half after linezolid therapy occurred in a male, thus clinicians must be aware of the potential of linezolid-induced encephalopathy, particularly in patients presenting risk factors (Fletcher et al., 2010). Clarithromycin has also induced an encephalopathy in adults characterized by symptoms appearing 1-10 days after drug intake and displaying clinical features ranging from delirium to non-convulsive status epilepticus (Bandettin di Poggio et al., 2011). Chinolones like ciprofloxacin and gemifloxacin are also reported to induce an encephalopathy (Rfidah et al., 1995; Barrett MJ 2009). Cephalosporine is reported to evoke an encephalopathy associated with a variety of electroencephalografic manifestations (Grill & Magati, 2008). Other cephalosporines such as cefuroxime, ceftazidime and cefazoline can result in an encephalopathy as well (Herishanu et al. 1988, Jackson et al., 1992; Ortiz et al., 1991). Cefoperazone is a cephalosporine that can cause a reversible encephalopathy characterized by triphasic waves in electroencephalography (Pro et al., 2011). Also penicillin-based antibiotics like penicillin itself, piperacillin and pivmecillinam caused an encephalopathy (Park-Matsumoto et al., 1996; Conway et al., 1968; Lokrantz et al., 2004).

2.3 Antiviral agents

Antiviral agents have seldom been reported to have induced an encephalopathy. As described in one case report, aciclovir can cause an encephalopathy. That patient had normal blood levels of aciclovir, and his renal function was normal (Delluc et al., 2004).

2.4 Antidepressants

Antidepressants can also result in an encephalopathy. The drug amitriptyline can cause an encephalopathy appearing as a neuroleptic malignant syndrome or a serotonin syndrome spectrum disorder (Miyaoka & Kamijama, 1995).

2.5 Anticonvulsants

The following anticonvulsants have been reported to induce a drug-induced encephalopathy: carbamazepine, gabapentin, levetiracetame, lamotrigine, phenytoine, primidone, topiramate, valproic acid and vigabatrine (Engel et al., 1971; Bauer & Elger, 1993; Hennessy & Miles, 1996; Garcia-Pastor et al., 2000; Sechi et al., 2004; Siniscalchi et al., 2004; Cheung et al., 2005; Horvath et al., 2005; Bauer, 2008). The most studied encephalopathy is valproic acid encephalopathy, which was first reported in epileptic and later psychiatric patients (Duarte et al., 1993; Settle, 1995). Valproic acid encephalopathy is often reversible after a week; prolonged time courses have been rare (Bauer & Elger, 1993). Antiepileptic drug-induced encephalopathies represent a seldom, but important side effect of antiepileptic drug therapy. There is an estimated 2% incidence of combined topiramate, valproate acid- induced hyperammonemic encephalopathy (Cheung et al., 2005). An average age of 38.6 years has been reported in a long-term study of valproic acid-induced encephalopathy (Gerstner et al., 2007).

2.6 Antineoplastic drugs and chemotherapeutics

Capecitabine is an antineoplastic drug replacing 5-Fluouracil in clinical practice. This drug can result in an encephalopathy with seizures even if a conventional dosis is used. No correlation was found between the encephalopathy development and a dihydropyridimidine dehydrogenase mutation (Fantini et al., 2010). Carmofur, a 5-fluorouracil derivative that induced a subacute leukencephalopathy, revealed an unsteady gait and dementia (Kuzuhara et al., 1987). A rare complication associated with cisplatin therapy is an encephalopathy with or without seizures (Steeghs et al., 2003). In particular, high doses of ifofosfamide can induce an encephalopathy. Ifofosfamide can result in myoclonus-encephalopathy syndrome (Savica et al., 2011). A cohort study revealed a prevalence of 10-40% of this drug-evoked encephalopathy. Female sex, low total albumin and haemoglobulin levels, as well as obesity appear to be risk factors associated with a ifofosfamide-evoked encephalopathy (Sweiss et al., 2008). There are few reports of the CNS toxicity of paclitaxel. Seizures have been reported in two patients. Little or no blood brain barrier penetration were the result of confusion and word-finding difficulties, and the encephalopathy resolved itself (Perry & Warner, 1996). Vincristine is known to be an agent that may lead to consecutive sensory and motor dysfunction and eventually fatal myeloencephalopathy (Fawaz al, 1992). Cyclosporine encephalopathy has also been reported (Kwon et al., 2008). Methotrexate has rarely led to an acute encephalopathy, its incidence is 0.8% in leukaemia or lymphoma and 4.5% in osteosarcoma or malignant fibrous histiocytoma (Inaba et al., 2008).

2.7 Immunosuppressants

An encephalopathy occurred after tacrolimus administration and improved after the drug was discontinued. It clinically depicted a right-sided hemiplegia with responsible lesions on diffusion-tensor imaging and diffusion-tensor tractography of the white matter tract (Kim et al., 2011). Sorafenib was reported to induce an encephalopathy in a patient with hepatocellular carcinoma (Dogan et al., 2010). Furthermore, a posterior, reversible leukoencephalopathy syndrome was observed after an infusion of infliximab (Zamvar et al., 2009).

2.8 Immunomodulators

Intravenous immunoglobulins (IVIG) can induce an acute encephalopathy probably caused by a cytotoxic brain oedema (Wada et al., 2005).

2.9 Neuroleptics and lithium

Lithium can to lead to an encephalopathy characterized by seizures, choreiforme as well as parkinsonian movements with cerebellar signs. Three risk factors contribute to lithium toxicity: a nephrogenic diabetes insipidus, age over 50 years, and thyroid dysfunction (Smith et al., 2003). Haloperidol can evoke an encephalopathy characterised by an electroencephalography (EEG) with characteristics of toxic encephalopathy (Maxa et al., 1997). The combination of lithium-risperidone induces an reversible encephalopathy (Boora & Hyatt, 2008). Two patients presented a prolonged postictal encephalopathy with clozapine-induced seizures (Karper et al., 1992) which lasted 63-72 hours and caused electroencephalographic abnormalities.

Drug	Dosage/d	Outcome after drug discontinuation	Reference
aciclovir	standard dosis	symptoms reversed after 72h	Delluc et al., 2004
capecitabine	2000mg/m²	improvement of symptoms	Fantini et al., 2010
carbamazepine	1200mg	symptoms and EEG normal after 2w	Horvath et al., 2005
ceftazidime	4g	symptoms resolved after a few days	Jackson et al., 1992
cefoperazone	2g	EEG and symptoms normal after 36h	Pro et al., 2011
dexamethasone	4mg p.o.	neuroimaging improvement after 4d	Irvin et al., 2007
Duodopa +entacapone	1200mg/d 76mg/h	100% mental status recovery after 48h	Manca et al., 2009
gabapentin	900mg	symptoms normalized after 4w	Sechi et al., 2004
gemifloxacin	320mg	full recovery 2d later	Barrett MJ 2009
isoretinoin	80mg	full recovery 24h later	Wong et al., 2010
IVIG	1000mg	full recovery after 11d	Wada et al., 2005
lamotrigine	400mg	symptoms normalized after 4w	Sechi et al., 2004
levetiracetame	3000mg	symptoms normalized	Bauer, 2008
lithium	400mg	symptoms resolved after 1 w	Smith et al., 2003
metronidazole	45.5g	symptoms improved within 6.7d	Kim et al., 2011
morphine	0,5mg	recovery after 10d	Eran & Barak, 2009
odansetron	4mg	full recovery of symptoms	Ritter et al., 2003
oxcarbazepine	1800mg	EEG and symptoms normalized after 20d	Siniscalchi et al., 2004
penicillin	i.v. 60 Mega Units	patient died	Conway et al., 1968
phenytoine	300mg	symptoms and EEG normalized	Engel et al., 1971
pivmecillinam	600mg	fast symptom recovery	Lokrantz et al., 2004
primidone	600mg	symptoms and EEG normalized after 2 w	Katano et al., 2002
propofol	150mg	recovery after 10d	Eran & Barak, 2009
sorafenib	400mg/2x	all symptoms resolved after 5d	Dogan et al., 2010
tacrolimus	0.1mg/kg/d	imaging abnormalities normalized after 4m	Kim et al., 2011
topiramate	1400mg	EEG and symptoms normalized after 7d	Cheung et al., 2005
valproic acid	2400mg	improvement in EEG and symptoms	Bauer & Elger, 1993
vigabatrine	3000mg	improvement in 2w	Garcia-Pastore et al., 2000

d = days, EEG = Electroencephalography, h = hours, IVIG intravenous immunoglobulines, m = month, w = weeks, p.o. = per os

Table 1. Drug-induced encephalopathy- clinics and outcome (not all drugs mentioned in the text are depicted in the table)

2.10 Other classes of drugs

There are several other classes of drugs that can result in a drug-induced encephalopathy. For instance, baclofen [a derivative of gamma-aminobutyric acid (GABA)] caused an encephalopathy with severe electroencephalographic abnormalities (Kumar et al., 2010). Another class of drugs such as duodopa (a combination of levodopa and carbidopa) has induced a reversible encephalopathy in Parkinson´s disease. An intermittent multifocal myoclonus was observed, and neurologic examination revealed a flaccid tetraparesis (Manca et al., 2009). An inadvertent injection of gadolinium (solutions of chelated organic gadolinium complexes) can result in grand mal seizures and mental changes due to an encephalopathy (Kapoor et al., 2010). This gadolinium encephalopathy probably occurred due to the inadvertent simultaneous entry of gadolinium and blood into the subarachnoid space. This case highlights the importance of using only a small amount of gadolinium. Agents like isoretinoin (medication in the therapy of Acne) may induce an encephalopathy with myoclonic jerks and confusion (Wong et al., 2010). Ondansetron (a 5-HT 3 receptor antagonist used mainly as an antiemetic drug) can produce a multifocal encephalopathy depicted by a transient pyramidal and extrapyramidal dysfunction with Babinski signs, oculogyric crisis, oromandibular and limb dystonia. The symptoms resolved after hours. Anaesthesiologists must take special care when administering ondansetrone therapy because of this rare complication and the severe clinical manifestation reflecting transient structural brain damage that however results in a full resolution of neurological symptoms. Sulfasalazine is a drug used primarily as an anti-inflammatory agent in the treatment of inflammatory bowel disease and rheumatoid arthritis. It has caused an encephalopathy characterised by cerebrospinal fluid with a high protein level (Mut et al., 2008).

3. Pathophysiological mechanisms

The underlying causes of a drug-induced encephalopathy are not yet fully understood. Several mechanisms of drug-induced encephalopathy are discussed below (table 3).

3.1 Cytotoxic and neurotoxic effects

There are several pharmaceutical cytotoxic and neurotoxic side effects that can cause an encephalopathy. A rise in the glutamine and glutamate complex peak in MR spectroscopy suggests for example an exitotoxic injury in the neurons and astrocytes in an acute IVIG-induced encephalopathy (Wada et al., 2005), and it is one possible mechanism inducing neurotoxicity.

3.2 Electrolytic disturbances

There are electrolytic disturbances such as a hypo-or hypernatremia that can promote drug-induced encephalopathy. Hyponatremia may be a side effect of drugs such as oxcarbazepine or diuretics. Severe hyponatremia is commonly caused by the syndrome of inappropriate antidiuresis (SIADH), which can also be induced by drugs like cyclophosphamide, vincristine, vinblastine, thiothixene, thioridazine, haloperidol, monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors and bromocripitine (Esposito et al., 2011). Hypopotassemia plays a role in the pathogenesis of convulsions and the high rate of mortality in theophylline encephalopathy (Suarez Ortega et al., 1995).

3.3 Hepatic enzyme interactions and hyperammonemia

Valproic acid can inhibit differential enzymes of the urea cycle, inducing a hyperammonemia (Sechi et al 2004, Treem et al., 1994). Moreover, there is the potential of damage on an enzymatic level that can lead to hyperammonemia: (1) carbamylphosphat synthetase-, (2) ornithin-transcarbamylase-, (3) N-acetylglutamat-synthetase-, (4) argininosuccinat-synthetase- and (5) arginino-succinat-lyase deficiency. As the incidence of these enzyme defects is low, valproic-acid encephalopathy very seldom has a hereditary cause. A high level of ammoniac can lead to hepatic necrosis in addition to encephalopathy. Hyperammonemia can be induced by the drugs depicted in table 2. Recent study data indicate that the hyperammonemia observed in patients under valproic-acid treatment is based on the direct inhibition of hepatic N-acetylglutamate synthase activity by valproyl-CoA (Aires et al., 2011). Hyperammonemia can induce an encephalopathy by inhibiting the glutamate uptake by astrocytes, thus provoking neuronal damage and cerebral oedema (Blindauer et al., 1998). Moreover, elevated extracellular glutamate reduces the size of the astroctyes, thereby inhibiting their function. The reduced synthesis of glutathione causes the neurons and glia cells to become more vulnerable to oxidative stress (Verotti et al., 2002). Finally, the over-production of glutamine leads to a swelling of the astrocytes followed by cerebral oedema and even higher cerebral pressure (Noremberg, 1996).

Drug	**Reference**
5-Fluouracil	Advani & Fakih et al., 2011
Acetazolamide	Kim et al., 2007
Carbamazepine	Adams et al., 2009
Haloperidol	Rubenstein et al., 1990
Lamotrigine	Fan et al., 2008
Primidone	Katano et al., 2002
Valproate acid	Aires et al., 2011
Zonisamide	Shaikh et al., 2009

Table 2. Drugs inducing hyperammonemia

An acute intermittent porphyria as one form of acute hepatic porphyria can present as a diffuse encephalopathy (Maramattom et al., 2005). Additionally, a mouse model has demonstrated that griseofulvin induces a hepatic porphyria characterized by psychiatric behavior sometimes observed in drug-induced encephalopathies (Satoh et al., 2008).

Drugs such as barbiturates, bernegride, chloramphenicol, chlordiazepoxide, chloroquine, chlorpropamide, danazol, diazepam, ergot preparations, estrogens, ethanol excess, griseofulvin, halothane, hydantoins, imipramine, ketamine, meprobamate, methyldopa, methyprylon, methsuximide, nikethamide, oral contraceptives, pentazocine, phensuximide, phenylbutazone, progestogens, pyrazinamide, pyrazolone derivatives, sulfonamides, theophylline derivatives, tolbutamide, troxidone and valproic acid (Bonkowsky et al., 1982) have been reported to exacerbate acute porphyrias. These drugs should thus be administered with caution in patients with an encephalopathy associated with porphyria. A further mechanism leading to an encephalopathy based on an increase in neuronal P450 CYP2E1 activity is induced by acetaminophen in an animal model (Posadas et al., 2010). Posadas et al. showed that acetoaminophen can result in a concentration-dependent neuronal apoptosis on rat cortical neurons through a mitochondrial-mediated mechanism

that includes cytochrome c release and caspase 3 activation (Posadas et al., 2010). Surprisingly, the neurotoxic action by acetoaminophen in rats is below those required to induce hepatotoxicity.

3.4 Effects on cerebral receptors

Effects on cerebral receptors play a important role as underlying pathomechanisms in drug-induced encephalopathy. The neurotoxicty in metronidazole encephalopathy is based on the RNA (Bradley et al., 1977) and DNA binding of intermediate metabolites of metronidazole (Wright & Tyler, 2003), modulating inhibitory GABA receptors in the cerebellar and vestibular systems (Evans et al., 2003).

Interaction with the GABA receptor plays a role in the intrinsic toxic effects of valproic acid encephalopathy (Miyazaki et al., 1988). Topiramate can induce a direct toxic effect on the central nervous system (CNS). Combined therapy with valproat acid produces this effect by reducing the metabolism of topiramate due to the interaction of valproic acid with the cytochrome-P450 effect. Gabapentin may cause a reversible encephalopathy clinically characterised by an asterixis. One candidate mechanism this encephalopathy is the agonistic interaction of gabapentin on cerebral GABA receptors in conjunction with increased inhibitory action (Fink et al., 2002). Cephalosporine-induced encephalopathy seems to involve GABA A receptor inhibition (Grill & Magati et al., 2008).

3.5 Metabolic effects

Severe diseases or malnutrition have a reduction in glucuron acid as a consequence. It is thus possible to inhibit the glucoronidation of valproate acid, resulting in a higher cumulative concentration of valproic acid, lamotrigine and oxcarbazepine in blood levels.

3.6 Vasogenic and cytotoxic brain oedema

Vasogenic and cytotoxic brain oedema as an underlying mechanism of a drug-induced encephalopathy is widespread. Metronidazole encephalopathy is probably caused by vasogenic and cytotoxic brain oedema. Most of the lesions in metronidazole encephalopathy correspond to areas of vasogenic oedema according to diffusion weighted imaging. Some lesions are located in the corpus callosum and correspond to cytotoxic oedema. Cytotoxic oedema is also a candidate mechanism in IVIG-induced encephalopathy. An intramyelinic oedema in the myelin sheath was observed in IVIG-induced encephalopathy (Wada et al., 2005). Many drug-induced encephalopathies share in common a posterior reversible leukoencephalopathy syndrome (PRES) possibly due to vasogenic oedema.

3.7 Posterior reversible leukoencephalopathy syndrome

The PRES has been described after the intake of immunosuppressants such as tacrolimus, cyclosporine or in association with acute hypertensive encephalopathy and eclampsia (Hinchey et al., 1996). It is characterised by capillary-leak syndrome in the brain caused by hypertension, liquid retention, immunosuppressants, and chemotherapeutics affecting the vascular endothelium. Clinical symptoms are headache, vomiting, confusion, seizures, cortical blindness and other visual symptoms. Neuroimaging reveals bilateral signal alterations in the posterior white mater suggesting oedema.

Candidate Mechanism	Drugs	Reference
cytotoxic brain edema	IVIG, metronidazole	Kim et al., 2011; Wada et al., 2005
effect on cerebral receptors	methotrexate	Sasazaki et al., 1992
electrolytic disturbance	theophylline	Suarez Ortega et al., 1995
hepatic enzyme interactions	valproic acid	Bauer & Elger,1993
hypoalbuminia	ifofosfamide	Sweiss et al., 2008
metabolic effects	lamotrigine, oxcarbazepine, valproic acid,	Bauer & Elger 1993, Hennessy & Miles, 1996
neurotoxic effect	IVIG	Wada et al., 2005
posterior reversible leukoencephalopathy syndrome	dexametha-sone, tacrolimus,	Kim et al., 2011; Irvin et al., 2007; Zhang, 2011
vasogenic brain edema	metronidazole	Kim et al., 2011

Table 3. Drug-induced encephalopathy-pathophysiological mechanisms

4. Pathological studies

Mild gliosis of the white matter and ischemic lesions in the temporal area were observed in a patient's postmortem analysis (Steeghs et al., 2003). Pathological-anatomic studies showed changes in the cerebellum and temporal lobe of predominantly the pyramidal and purkinje cells in rats after chronic administration of valproate acid (Sobaniek-Lotowska, 2003). Those studies reported damage to the hippocampal astrocytes and neocortex. All these abnormalities seemed to disappear three months after discontinuation of the drug.

5. Genetic susceptibility

A further factor contributing to the development of a drug-induced encephalopathy is genetic susceptibility. The individual´s genetic patrimony including ethnicity and gender influences the susceptibility to the risk of a drug-induced encephalopathy. Any genetic polymorphism may influence the metabolism, excretion or action of the drug depending on single or multiple genes or by changes in gene expression (Dodd et al., 2004). For instance, some mutations can promote development of an encephalopathy, i.e. a mutation in ETHE1, a mitochondrial matrix sulphur dioxygenase causing an ethlymalonic encephalopathy (Viscomi et al., 2010). In a patient with the rare missense variant methionine synthetase c.2756A>G (D919G), a methotrexate encephalopathy was observed probably due to a modified effect of methotrexate on homocysteine metabolism (Linnebank et al., 2007). A recent clinical study showed that the genetic polymorphism of the human thymidylate synthetase gene contributes to 5-fluorouracil-associated hyperammonemic encephalopathy. A GABA A receptor modification caused by knockout of the taurine transporter resulted in striatal disinhibition in mice. This animal study demonstrates that a genetic defect ending up in a lack of taurine partly explains the pathophysiology of a hepatic encephalopathy (Sergeeva et al., 2007). Mitochondrial dysfunction underlies different types of encephalopathy, for example, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). As an example, the mutation of mitochondrial DNA (mtDNA) G13513A encoding the ND5 subunit of

respiratory chain complex 1 causes mitochondrial encephalopathy with lactic acidosis (Wang et al. 2008). Therefore, supplementation with the mitochondrial respiratory chain cofactor coenzyme Q10 has been demonstrated to advance recuperation following heroin-induced encephalopathy (Gacouin et al., 2003).

6. Epidemiology

The epidemiology of ifofosfamide encephalopathy is well known. Ifofosfamide encephalopathy occurred in 31.2% of patients with soft tissue and bone sarcomas (17/61) treated with ifofosfamide, and in 13.6% of ifofosfamide treatment courses. A history of cisplatin was identified as a potential risk factor for the development of an ifofosfamide-induced encephalopathy (Tajino et al., 2010). Furthermore, a dose of ifofosfamide at >9g/m^2 is a further risk factor of ifofosfamide-induced encephalopathy (Tajino et al., 2010). In other previous studies, risk factors such as large tumors in the female pelvic cavity (Meanwell et al., 1986), poor performance status (Antman et al., 1989), hypoalbuminemia (Merimsky et al., 1992), high serum creatinine level (Antmann et al., 1990) and low iron bicarbonate level (Antmann et al., 1989) were identified as risk factors for ifofosfamide-induced encephalopathy. It remains controversial as to whether there are risk factors of ifofosfamide-induced encephalopathy, as another study showed no risk factors associated with this encephalopathy and that each patient has his own predisposition (Rieger et al. 2004). Alcoholism was identified as a risk factor in linezolide-induced encephalopathy (Fletcher et al., 2010). Renal failure and previous central nervous system disease may predispose to ceftriaxone- and cefepime-induced encephalopathy (Roncon- Albuquerque et al., 2009; Garces et al. 2008). Dialysis may be a risk factor in isoniazide-induced encephalopathy (Cheung et al. 1993). There are common risk factors affecting the neuronal health for different types of drug-induced encephalopathies such as environmental toxins, infectious diseases, traumatic events, brain tumors, brain ischemia, age (state of health, disease), nutritional deficiencies and intolerances, and even poverty (Virmani et al. 2010).

In conclusion, not everyone develops an encephalopathy after taking a certain drug, but those individuals who are at risk (see above) - although the extent and nature of the risk are often unknown - may be more apt to develop an encephalopathy.

Patients with metronidazole encephalopathy showed a mean age of 61 years (49-71 years) (Kim et al., 2007), whereas those with clarithromycin encephalopathy exhibited an average age of 51 years (19-87 years) (Bandetti di Poggio et al., 2011). These data are based on case series, and there are no long-term clinical studies addressing the epidemiology of drug-induced encephalopathies. In a cohort study of 19 patients, 8 patients (42%) developed an ifofosfamide induced encephalopathy (Sweiss et al. 2008). The exact prevalence of a drug-induced encephalopathy is unknown, as case series with calculated epidemiologic data are rare. Furthermore, there are no studies larger in scale examining the specific age of a drug-induced encephalopathy. The average age for valproic-acid encephalopathy was 38.6 years in a long-term study (Gerstner et al. 2007).

Toxic encephalopathies are accompanied by high blood levels of the suspected drug, whereas drug-induced encephalopathies often reveal therapeutic blood levels of the drug. Thus we know of no dose-dependent effect of drugs that induce an encephalopathy. The symptoms can develop from within hours until a month after taking the drug.

7. Basic clinical features

The clinical spectrum of symptoms can result in slight disturbances of the mental state up to severely damaged consciousness (table 4). Transient acute encephalopathy has been observed in 3-15% of cancer patients after methotrexate therapy (Rubnitz et al. 1998). Chronic encephalopathy develops slowly, may progress, and can permanently impair neurological function. A drug-induced encephalopathy may reveal a varied spectrum of psychiatric symptoms, i.e. hallucinations (Sorafenib; Dogan et al., 2010), psychotic state (vigabatrine; Garcia-Pastore et al., 2000), depression (sodium valproate, Connacher et al., 1987) and neuropsychologic symptoms like reduced psychomotor speed and impaired working memory (levetiracetame, valproic acid; Bauer et al., 2008). The development of psychiatric symptoms may be acute, subacute or chronic.

Clinics	Drugs	Reference
abnormal sensation	metronidazole	Wada et al., 2005
aggravation of preexisting neurological deficits	carbamazepine, gabapentine, levetiracetame, lamotrigine, oxcarbazepine, primidone, topiramate	Bauer, 2008; Hennessy & Miles, 1996, Horvath et al., 2005; Katano et al., 2002; Latour et al., 2004; Siniscalchi et al., 2004; Sechi et al., 2004
altered consciousness, concentration	capecitabine, gabapentine, IVIG, lithium, valproic acid	Bauer & Elger 1993; Fantini et al., 2010; Katano et al., 2002; Sechi et al., 2004
anisocoria, diplopia	dexamethasone	Irvin et al., 2007
aphasia	carbamazepine, topiramate	Horvath et al., 2005, Latour et al., 2004
ataxia, apraxia	capecitabine, carbamazepine, phenytoine, topiramate, valproic acid	Fantini et al., 2010, Horvath et al., 2005
choreiform movements, athetosis	tiagabine, trimetazidine,	Sivet et al., 2008; Tombini et al., 2006
delirium, coma	carmofur	Kuzuhara et al., 1987
dementia, memory loss	carbamazepine, carmofur, gabapentine, levetiracetame	Bauer, 2008; Horvath et al., 2005, Kuzuhara et al., 1987; Sechi et al., 2004
dysathria	metronidazole, lithium, tacrolimus,	Smith et al., 2003; Wada et al., 2005,
gait disturbance	carmofur, sorafenib, trimetazidine,	Dogan et al., 2010; Kuzuhara et al., 1987; Sivet et al., 2008
headache	paclitaxel	Perry & Warner, 1996
myoclonias	carbamazepine, levetiracetame, odansetrone, vigabatrine, lithium	Bauer, 2008; Garcia-Pastor et al., 2000; Horvath et al., 2005, Ritter et al., 2003; Smith et al., 2003

oculogyric crisis, oromandibular and limb dystonia	odansetrone	Ritter et al., 2003
parkinsonism	carbamazepine	Horvath et al., 2005
psychiatric symptoms	valproic acid, sorafenib, levetiracetame, vigabatrine	Dogan et al.2010; Garcia-Pastor et al., 2000; Bauer, 2008
ptosis	dexamethasone	Irvin et al., 2007
seizures	cisplatin, cyclosporine, gadolinium levetiracetame, valproic acid, vigabatrine	Bauer, 2008; Bauer & Elger, 1993, Dzudie et al., 2009; Garcia-Pastor et al., 2000; Kapoor et al., 2010; Steeghs et al., 2003;
sleep disturbance, hypersomnia, insomnia	capecitabine, carbamazepine, topiramate	Cheung et al., 2005, Fantini et al., 2010, Horvath et al., 2005, Cheung et al., 2005
stupor, agitated state	morphine	Eran & Barak, , 2009
tremor	tacrolimus	Kim et al., 2011
vertigo	sorafenib, valproic acid	Bauer & Elger, 1993; Dogan et al., 2010
visual symptoms, nystagmus	metronidazole, phenytoine, primidone, trimetazidine, sorafenib, topiramate	Wada et al., 2005; Dogan et al., 2010; Engel, 1971, Katano et al., 2002, Latour et al., 2004; Sivet et al., 2008;
vomiting, nausea	valproic acid	Bauer & Elger, 1993

Table 4. Drug-induced encephalopathy- Clinics

8. Diagnostics

8.1 Electrophysiologic studies

EEG has often revealed signs of encephalopathy. The main characteristics are a diffuse, unusually mild to heavy general changes (Horvath et al., 2005, Tombini et al., 2006). Triphasic waves with intermittent frontal delta activity are sometimes observed (Gallmetzer et al., 2004; Rancon-Albuquerque et al., 2009). Focal and generalised slow waves, and generalised or focal epileptic spike-wave complexes have also been seen. Once the responsible drug is discontinued, the encephalopathy with general slowing and epileptic discharges resolve after days or weeks, sometimes after months (Bauer & Elger, 1993; Latour et al., 2004).

8.2 Laboratory investigations

The effective concentration of the drug in sera is often within the normal range in patients with valproic acid-induced encephalopathy (Bauer & Elger, 1993), whereas higher concentration of the drugs were noted in carbamazepine (Neumann et al. 1994) and lamotrigine encephalopathy (Hennesy & Miles, 1996). When clinical signs and symptoms of

a drug-induced encephalopathy are present, relevant clinical routine tests for natremia, ammonemia or glycemia should always be performed to identify the reason for the encephalopathy and develop a treatment strategy. A hypoglycemic encephalopathy can be detected by measuring the blood glucose level, thereby differentiating it from drug-induced encephalopathies. The clinical spectrum of hypoglycemic encephalopathy ranges from simple neurological deficits and mental changes to severe coma and death (Lo et al., 2006). A specific lesion pattern is frequently detected in hypoglycemic encephalopathy, often affecting the cerebral cortex, basal ganglia, hippocampus, splenium and bilateral internal capsula (Aoki et al., 2004; Chan et al., 2003; Terakawa et al., 2007; Cho et al., 2006). This selective vulnerability in hypoglycemic encephalopathy may be associated with the extent to which the metabolism necessary to conserve the function of brain structures and neuronal integrity has been compromised (Lee et al., 2011).

8.3 Imaging patterns

Cerebral atrophy has been observed in valproic-acid encephalopathy, especially in chronic encephalopathy as some authors have described in cranial computertomography (CT) and magnetic resonance imaging (MRI) (Baganz et al., 1994; Papazian et al., 1995). Lacunar lesions were found in gabapentin-induced encephalopathy (Sechi et al., 2004). Metronidazole-induced encephalopathy induced bilateral symmetric T2-hyperintense lesions in the cerebellar dentate nucleus, midbrain, dorsal pons, medulla, and splenium of the corpus callosum. Except for the corpus callosum, all lesions were irreversible. The lesions are often bilateral and symmetric. High signal intensity in T2-weighted images appeared, but the signal alterations did not demonstrate contrast enhancement and were reversible after drug discontinuation. Dexamethasone encephalopathy in MRI resulted in diffuse cortical and subcortical white matter lesions in symmetric bilateral distribution involving predominantly occipital areas, the cerebellum and focal areas of bilateral thalami not evident in the T1-weighted images characteristic of PRES. In cyclosporine-induced encephalopathy, the lesions show vasogenic oedema apparently in diffusion coefficient maps (Bartynski et al., 2007). Some imaging pattern are shown in table 5.

Anatomic lesion pattern	**Drugs**	**Reference**
bilateral temporal periventricular white-matter lesions	sulfasalazine	Mut et al., 2008
centrum semi-oval atrophy	tacrolimus	Kim et al., 2011
cerebellum	metronidazole	Kim et al., 2011
corpus callosum	metronidazole	Kim et al., 2011
cortical and subcortical parietal, occipital and frontal white matter lesions	dexamethasone, IVIG	Irvin et al., 2007; Wada et al., 2005
deep white matter lesions	capecitabine, paclitaxel	Fantini et al., 2010; Perry & Warner, 1996
midbrain, pons, medulla lesions	metronidazole	Kim et al., 2011

Table 5. Neuroimaging of drug-induced encephalopathies

9. Differential diagnosis

The most important differential diagnosis of metronidazole-induced encephalopathy is Wernicke encephalopathy. In the early stages of the disease, the two entities may be confounded because they can produce similar clinical features. In metronidazole-induced encephalopathy (unlike Wernicke encephalopathy), lesions of cerebellar dentate nuclei are supported by pathological studies (Troncoso et al., 1981). Further differential diagnoses are acute infectious encephalitis and demyelinating disease including Marchiafava-Bignami disease. Other types of encephalopathies must be differentiated from drug-induced encephalopathies such as hepatic, heavy metal, uremic, septic, and mitochondrial encephalopathy.

10. Therapeutic options

Therapy consists in the immediate discontinuation of the suspected drug when first signs of encephalopathy appear. A complete reversal of symptoms should take place soon after drug discontinuation. The atrophy in valproate-induced encephalopathy can also be reversed in individual cases. The administration of L-carnitine makes therapeutic sense in cases of carnitine deficiency (Kelley, 1994). Intravenous carnitine was recently shown to be useful in the treating hyperammonemic encephalopathy (Bøhmer & Hoymork, 2010). Moreover, the treatment of a valproate-induced encephalopathy via haemodialysis has succeeded (Tsai & Chen, 2008). Short-term hemodialysis often helps to reverse the symptoms in cefepime encephalopathy (Lin et al., 2011). Drug-induced encephalopathy often has a good prognosis. Methylen blue is an therapeutic option for an ifosfamide-induced encephalopathy (Patel, 2006). A drug-induced encephalopathy can sometimes be prevented by adjusting the dosage and monitoring serum concentrations of the suspected drug. Normally the blood level of the suspected drug is within the therapeutic range, so that treating an overdose would make no sense. Only in particular situations are certain measures to treat overdoses necessary, i.e. gastric lavage, activated charcoal, hemodialysis, hyperhydration or forced diuresis.

11. Conclusions

Several drugs can induce drug-induced encephalopathies. They seldom occur in clinical practice, but are important pharmacological side effects. Drug-induced encephalopathies are a key differential diagnosis when a disturbance of the consciousness is initially unclear. The effective levels of the drug in the blood often fall within the reference and not in the toxic range. Effective therapy consists in immediately discontinuing the drug.

12. References

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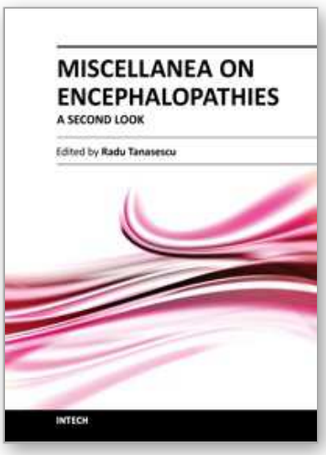

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