Published in final edited form as:

J Clin Neurophysiol. 2013 October ; 30(5): . doi:10.1097/WNP.0b013e3182a73db9.

The electroencephalography of encephalopathy in patients with endocrine and metabolic disorders

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Abstract

Patients with acute alteration in mental status from encephalopathy due to underlying metabolic-toxic or endocrine abnormalities are frequently seen in the acute hospital setting. A rapid diagnosis and correction of the underlying cause is essential as a prolonged state of encephalopathy portends a poor outcome. Correct diagnosis and management remain challenging because several encephalopathies may present similarly, and further laboratory, imaging or other testing may not always reveal the underlying cause. Electroencephalography (EEG) provides rapid additional information on the encephalopathic patient. It may help establish the diagnosis, and is indispensable for identifying non-convulsive status epilepticus – an important possible complication in this context. The EEG may assist the clinician in gauging the severity of brain dysfunction, and may aid in predicting outcome.

This review summarizes the current knowledge on EEG findings in selected metabolic and endocrine causes of encephalopathy, and highlights distinct EEG features associated with particular etiologies.

Keywords

EEG; encephalopathy; altered mental status; delirium; endocrine disorders

Introduction

The term encephalopathy typically refers to the reversible global change in brain function manifesting with attentional impairment, sleep-wake cycle disturbances, deficits in memory and mental data processing, and changes in arousal (hyper- or hypoactive). Encephalopathy frequently occurs in the elderly and in hospitalized patients, is particularly common in the intensive care unit (ICU), and is associated with poor outcome (Ely et al., 2004; Witlox et al., 2010). The most common causes of encephalopathy are systemic illnesses in the setting of infection, hypoxic-ischemic brain injury, and metabolic-toxic states due to single- or multi-organ dysfunction. Electrolyte imbalance, vitamin deficiencies, and endocrine

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Conflicts of interest

None of the authors has relevant conflicts of interest, except authorship in several books on EEG from P.W.K.

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disorders may be sole or contributory causes of encephalopathy, and elderly and hospitalized patients frequently present with complex medical problems that involve several organ systems. The clinician must then discern which of the many pathologic conditions is most contributory to the patient's confusional state (Kaplan, 2004).

The electroencephalogram (EEG) is readily available, relatively cheap, and the most widely used technique to detect and monitor electrocerebral activity (Hooshmand and Maloney, 1980). In the evaluation of the encephalopathic patient, EEG may help in differentiating organic from psychiatric conditions, and is the only tool that can diagnose nonconvulsive status epilepticus (NCSE). Furthermore, EEG may help determine the severity of the underlying brain dysfunction, and may assist in predicting clinical outcome (Kaplan, 2004). While the EEG lacks specificity in differentiating among the various metabolic encephalopathies, discernable EEG patterns along with clinical history and imaging findings may provide helpful information to the clinician regarding underlying etiologies. Testing for endocrine or metabolic causes of encephalopathy may not be part of the routine work-up in most emergency rooms or hospitals, and therefore an EEG may help guide further evaluation of encephalopathy beyond the routine studies.

Here, we review current knowledge on EEG findings associated with metabolic derangements, and describe the different EEG patterns found in encephalopathies resulting from electrolyte disorders, hormonal disturbances, and other selected metabolic disorders. Furthermore, we discuss the different causes of mental status changes seen with various metabolic disorders, and highlight the role of EEG in identifying the underlying etiology. Table 1 presents a summary of EEG findings associated with the etiologies of encephalopathy discussed in this review.

Endocrine Disorders

Hyperthyroidism—The continuum of central nervous system (CNS) symptoms associated with various degrees of hyperthyroidism ranges from subtle impairment of cognitive function, insomnia, emotional lability and anxiety, to severe and potentially life threatening manifestations, such as severe encephalopathy, seizures and coma (McDermott, 2012). The latter is most frequently encountered during *thyroid storm* which has a mortality rate of up to 20% (McDermott, 2012). There is no clear correlation between the degree of EEG abnormality and serum thyroid hormone level (Leubuscher et al., 1988). An increase in frequency of the posterior dominant rhythm, an increase in fast activity, as well as a higher incidence of theta and delta activity have been observed in thyrotoxicosis, and in experimental hypermetabolism (Rubin et al., 1937; Vague et al., 1952; Condon et al., 1954; Vague et al., 1957). High-voltage and prolonged EEG responses to photic stimulation have also been described (Wilson et al., 1964). Wilson et al. noted that these changes were most profound in young women (Wilson et al., 1964). Rarely, triphasic waves (TWs) have been reported in patients with acute hyperthyroidism (Scherokman, 1980; Hirano et al., 1982). A case of *thyrotoxic storm* presenting as posterior reversible encephalopathy syndrome (PRES) in a patient with generalized convulsions and coma, has been described, however, PRES associated with hyperthyroidism is exceedingly rare (Homma et al., 1999). Hyperthyroidism lowers seizure threshold in patients with preexisting epilepsy (Wilson et al., 1964; Izumi and Fukuyama, 1984). Furthermore, *de novo* convulsive seizures in the setting of thyrotoxicosis are well recognized (Korczyński and Bechar, 1976; Jabbari and Huott, 1980; Safe et al., 1990; Su et al., 1993; Obeid et al., 1996; Maeda and Izumi, 2006). Thyrotoxicosis presenting as new-onset seizures is often refractory to antiepileptic drugs (AEDs), and may only be controlled after reaching an euthyroid state (Jabbari and Huott, 1980; Safe et al., 1990; Su et al., 1993). In a case report of a patient with iatrogenic hyperalimentation with levothyroxine, the EEG revealed NCSE with almost continuous

bisynchronous spike-and-wave discharges with an occipital predominance (Sundaram et al., 1985).

Hypothyroidism—In the adult, symptoms of hypothyroidism range from mild cognitive slowing and memory impairment to stupor and coma, referred to as myxedema (Casaletto, 2010). The EEG in hypothyroid adults may be entirely normal, but in more severe cases, the EEG may show a slow posterior basic rhythm (Hermann and Quarton, 1964), as well as low-voltage activity predominantly in the theta and delta range (Nieman, 1959; Lansing and Trunell, 1963) with poor or absent EEG background reactivity to noxious stimuli (Scarpalezos et al., 1973). TWs (River and Zelig, 1993) and generalized periodic sharp waves resembling Creutzfeld-Jacob Disease have been described (Nieman, 1959; Lansing and Trunell, 1963; Hermann and Quarton, 1964). Rarely, frontal intermittent rhythmic delta activity (FIRDA) occurs (Schaul et al., 1981). In infants with congenital hypothyroidism, there is a delay in development of the EEG phenomena of sleep, particularly sleep spindles (Schultz et al., 1968).

Hypercortisolism—EEG changes due to hypercortisolism have been studied in patients with Cushing syndrome, either due to endogenous adrenal cortical hyperfunction, or after iatrogenic administration of prednisone or adrenocorticotrophic hormone (ACTH). While the EEG may remain entirely normal in many patients (Pine et al., 1951), slowing of the EEG background activity in the theta/delta range has been observed (Hoefer and Glaser, 1950; Glaser et al., 1955). Conversely, excessive fast activity has been described, occasionally with frequencies up to 35 Hz (Krankenhagen and Penin, 1970). In patients with preexisting epilepsy, an increase in seizure discharges has been described after exogenous corticosteroid administration (Glaser et al., 1955). PRES from excessive corticosteroids has been reported in a six year-old girl with seizures and magnetic resonance imaging (MRI) showed typical signs of PRES in the setting of bilateral adrenal hyperplasia (Lodish et al., 2010). With bilateral adrenalectomy, the MRI changes resolved, and the patient remained seizure free.

Hypocortisolism—The EEG in Addison disease may be entirely normal with milder presentations, however, in more severe forms, the recording can be disorganized with slowing of the posterior dominant rhythm below the alpha range (Engel, G.L., Margolin, S.G., 1942), and blocking of the basic rhythm during eye opening is frequently lacking (Kollmannsberger et al., 1969). Furthermore, early reports describe generalized high-voltage activity in the theta/delta range (Skanse and Nyman, 1958; Mera, 1967). It should be noted that it is difficult to discern whether observed EEG changes are solely due to the lack of corticosteroids since hypocortisolism is frequently accompanied by other concomitant metabolic abnormalities, such as hypoglycemia and hyponatremia. Interestingly, the EEG in a patient with isolated ACTH deficiency in coma but without concomitant hypoglycemia, hyponatremia, or systemic hypotension was remarkable for bilateral, rhythmic high-amplitude sharp and slow wave complexes with a postero-anterior lag, predominantly in the frontal leads (Sugita et al., 2012). The authors postulated either a TW encephalopathy, or NCSE.

Hyperglycemia—Hyperglycemia is associated with a wide range of neurological symptoms, including focal neurological symptoms, myoclonus, seizures, vestibular dysfunction, and encephalopathy (Maccario et al., 1965). The encephalopathy observed in hyperglycemia can range from mild confusion and disorientation, to coma depending on the degree of hyperglycemia and hyperosmolarity. The EEG is largely normal until serum glucose concentrations exceed 400 mg/dl. Initially, the EEG is characterized by mixed slow and fast activity with some epileptiform activity (Gibbs et al., 1940). However, with increasing serum glucose concentrations, diffuse and often continuous medium to high

voltage theta-delta activity predominates (Maccario, 1968). When hyperglycemia is associated with clinical seizures, EEG findings include paroxysmal focal spike-wave discharges, focal medium to high-voltage theta/delta transients, and synchronous generalized slow bursts (Maccario, 1968). Periodic lateralized epileptiform discharges (PLEDs) in the setting of acute cerebral ischemia are more frequently found in patients with concomitant hyperglycemia as compared to normoglycemic patients (Neufeld et al., 1997). This suggests that while a structural lesion is required for the appearance of PLEDs, the latter may be triggered by the interplay of structural and metabolic derangements, such as hyperglycemia. Young et al. described a patient with left-hemispheric PLEDs followed by time locked *nystagmus retractorius* in the setting of severe hyperglycemia in the absence of a detectable brain lesion on CT (Young et al., 1977). However, since this case was reported before the “MRI-era”, it remains unclear whether there may have been signs of structural brain abnormalities not apparent on CT. A retrospective study found that among hospitalized patients who had EEG findings with FIRDA, almost one third were hyperglycemic at the time of the recording, however, the degree of hyperglycemia and glucose levels were not specified (Waternberg et al., 2002). Neurologic complications, in particular seizures and NCSE, are more commonly associated with non-ketotic rather than ketotic hyperglycemia (Dibenedetto et al., 1965; Maccario et al., 1965; Vastola et al., 1967; Daniels et al., 1969). While hypoglycemia-induced seizures are usually generalized, seizures associated with hyperglycemia are predominantly focal. There have been several reports of focal motor seizures with and without disturbance of consciousness in patients with severe non-ketotic hyperglycemia (Singh et al., 1973; Manford et al., 1995; Cokar et al., 2004). Since both NCSE and metabolic abnormalities with hyperglycemia cause mental status changes, confusion, and depression of consciousness, a contribution of seizure activity to mental status changes in a hyperglycemia patient may not be apparent without an EEG. The importance of an EEG to distinguish whether subtle mental status changes in hyperglycemia patients are due to NCSE, or to metabolic derangements alone is highlighted by several recent reports. One case series described a patient with non-ketotic hyperglycemia who presented in NCSE of frontal origin clinically manifesting with euphoria, disinhibition, attention deficits, and executive dysfunction (Thomas et al., 1999). In a recent case report of a patient with non-ketotic hyperglycemia, the EEG revealed NCSE clinically characterized only by a fluctuating language disorder (Pro et al., 2011). Similarly, a case of a patient with pure alexia without agraphia due to NCSE in the setting of hyperosmolar, non-ketotic state was described (Kutluay et al., 2007) (Figure 1). Hyperglycemia-associated seizures are frequently refractory to AEDs unless the underlying hyperglycemia and concomitant metabolic abnormalities are promptly corrected (Maccario, 1968; Lavin, 2005).

Hypoglycemia—Hypoglycemia manifests with autonomic symptoms such as diaphoresis, tachycardia, tremulousness, and generalized weakness, focal neurological deficits, and with a continuum of mental status disturbances ranging from disorientation and confusion, to coma depending on the degree and time-course of the hypoglycemic state (Virally and Guillausseau, 1999). Symptomatic hypoglycemia rarely occurs with serum glucose levels above 55 mg/dl in healthy adults and 70 mg/dl in diabetics (Virally and Guillausseau, 1999; Cryer et al., 2009). Correction of hypoglycemia is usually accompanied by resolution of symptoms, however, occasional neurologic symptoms may linger even after reaching normoglycemia (Cryer, 2007). There may be no clear correlation between EEG changes, glucose level, and level of consciousness (Gellhorn and Kessler, 1942). An early study demonstrated that asymptomatic and awake patients may have normal EEGs, even in the presence of profound hypoglycemia (Ziegler and Presthus, 1957). Several authors have noted slowing of the posterior basic rhythm below the alpha range in EEG recordings of awake and fully conscious patients with blood glucose levels below 70 mg/dl (Davis, 1943; Brazier et al., 1944), while more severe hypoglycemia is accompanied by diffuse theta

activity in the unconscious patient (Figure 2). Interestingly, while the increase in theta and delta activity during mild hypoglycemia with serum glucose levels between 50 and 60 mg/dl reaches its topographic maximum in the frontal region, the maximum of slow frequencies during more profound hypoglycemia is found in the centro-temporal and parieto-occipital regions (Tribl et al., 1996). Occasionally, a FIRDA pattern may be observed in hypoglycemic patients (Schaul et al., 1981). Epileptiform discharges have been described during hypoglycemia particularly in patients with diabetes mellitus (Bjorgaas et al., 1998), and accentuation of focal temporal spikes or sharp waves was seen at serum glucose levels below 45 mg/dl in patients with a known history of complex-partial seizures (Sperling, 1984). Rarely, PLEDs may be seen in hypoglycemia (Schraeder and Singh, 1980). There have been several reports of hypoglycemia due to insulinoma mimicking various seizure types, or epilepsy syndromes. Wang et al. describe a patient without prior history of seizures who presented with clinical features resembling complex partial seizures refractory to multiple AEDs during insulinoma-related hypoglycemia. An interictal EEG showed left temporal spikes and sharp waves, and an EEG tracing during one of these episodes showed build-up of diffuse high-voltage theta and delta activity as well as sporadic spikes and sharp waves. Rapid glucose administration terminated one of the typical episodes and resulted in normalization of the EEG (Wang et al., 2008). Insulinoma mimicking juvenile myoclonic epilepsy was described in an adolescent with myoclonus and generalized tonic-clonic seizures (GTCS) upon awakening. The EEG during sleep showed generalized polyspikes and slow waves (Jaladyan and Darbinyan, 2007). After surgical removal of the insulinoma, the patient remained seizure-free without any AEDs. In yet another case of insulinoma mimicking a refractory seizure disorder, the EEG revealed a gradual build-up of diffuse slow waves immediately prior to the attack, followed by a few anterior spikes and sharp waves. EEG changes normalized after administration of glucagon (Graves et al., 2004).

Electrolyte Disorders

Hyponatremia—Hyponatremia is one of the most common electrolyte abnormalities, affecting as much as 2.5% of hospitalized patients. The severity of central nervous system (CNS) manifestations is mainly dependent on the rapid fall of serum sodium levels, rather than on absolute values (Fried and Palevsky, 1997). Initial symptoms include nausea, headache, confusion, and agitation, and as sodium levels decrease further, seizures, coma, respiratory arrest and death ensue (Casaletto, 2010). EEG changes do not always correlate with absolute serum sodium levels, and changes in serum sodium have a more profound effect on the EEG when they are of rapid onset (Rebelo et al., 1971). Initial slowing of the posterior basic rhythm (Rebelo et al., 1971) is followed by more diffuse slowing in the delta range (Okura et al., 1990), and the EEG may remain abnormal for some time even after prompt correction of the electrolyte abnormality (Zwang and Cohn, 1981; Reddy and Moorthy, 2001). Furthermore, central high-voltage activity in the theta range with stimulation-induced paroxysms of delta waves (Crawford and Dodge, 1964), and periodic delta waves appearing diffusely over a background rhythm of theta activity have been described (Nakayama et al., 1999). Although rare, TWs (Bahamon-Dussan et al., 1989; Maruyama et al., 1991) and PLEDs (Itoh et al., 1994) have been reported in hyponatremic patients. Ragoschke-Schumm et al. describe a 16 year-old boy with desmopressin-induced hyponatremia resulting in a transient FIRDA pattern on EEG (Ragoschke-Schumm et al., 2005). Similarly, Kameda et al. report a case of FIRDA in a patient with hyponatremic encephalopathy and pituitary adenoma (Kameda et al., 1995), possibly due to the adenoma rather than the hyponatremia. There have been several reports describing patients without a preexisting seizure history presenting with a severe encephalopathy from NCSE due to hyponatremia (Thomas et al., 1992; Primavera et al., 1995; Azuma et al., 2008). Several different EEG features have been described in patients presenting with *de novo* NCSE due to hyponatremia. Of note, EEGs in hyponatremia-associated NCSE predominantly reveal

generalized epileptiform activity (Thomas et al., 1992; Primavera et al., 1995). Azuma et al. report a case of *de novo* NCSE due to hyponatremia with an ictal EEG showing continuous and bilateral spike and slow wave activity, however, a follow-up EEG after recovery from NCSE revealed left-sided focal spikes, suggesting that onset was focal with secondary generalization (Azuma et al., 2008). Table 2 provides a summary of EEG findings with hyponatremia.

Hypercalcemia—Neurologic symptoms with hypercalcemia most commonly include alteration of mental status, irritability, depression, lethargy, confusion, and rarely coma (Riggs, 2002; Castilla-Guerra et al., 2006). The main determinant of the degree of cognitive impairment is the rapidity of hypercalcemic change, rather than the absolute serum calcium level (Marx, 2000). EEG changes appear at serum calcium levels above 12-13 mg/dl (Spatz et al., 1977; Juvarra et al., 1985). Most commonly, the EEG shows diffuse slowing of the posterior basic rhythm (Bogdonoff et al., 1956; Edwards and Daum, 1959; Lynch et al., 1964). In a case series of 8 patients with symptomatic hypercalcemia of various etiologies, all patients had similar EEG patterns, such as a diffuse slowing with paroxysms of frontal dominant, moderately high-voltage activity in the theta/delta range (Moure, 1967) - findings that were later corroborated in several larger case series (Evaldsson et al., 1969; Allen et al., 1970; Cohn and Sode, 1971; Swash and Rowan, 1972). Additionally, unusual prominent lambda waves can be seen in hypercalcemia even in non-alert patients (Allen et al., 1970), and occasionally TWs (Swash and Rowan, 1972) and PLEDs (Kaplan, 1998) can be seen. EEG abnormalities in hypercalcemia generally normalize with correction of hypercalcemia, although some authors report a delay in EEG normalization (Allen et al., 1970). Clinical seizures and epileptiform activity on EEGs in patients with symptomatic hypercalcemia are exceedingly rare, since elevated serum calcium levels cause CNS depression and reduced neuronal membrane excitability. However, if epileptiform activity is described, it seems to predominate over the parieto-occipital regions (Huott et al., 1974; Chung et al., 2005), and a vasospastic effect in the posterior circulation associated with high calcium levels has been postulated (Kaplan, 1998) (Figure 3). There have been a few reports on encephalopathic patients in the setting of hypercalcemia-associated PRES, even without evidence of hypertension (Kastrup et al., 2002; Choudhary and Rose, 2005; Kim et al., 2005; Ma et al., 2009). EEG changes included generalized slowing (Choudhary and Rose, 2005), and occipital intermittent rhythmic delta activity (OIRDA) (Kastrup et al., 2002), however, no epileptiform activity was described.

Hypocalcemia—The most common etiology of symptomatic hypocalcemia is uncontrolled hypoparathyroidism. CNS manifestations of acute hypocalcemia include seizures and mental status changes, such as irritability, agitation, confusion, depression and psychosis (Fonseca and Calverley, 1967; Riggs, 2002). Hypocalcemia is one of the most epileptogenic electrolyte disturbance with seizures reported in as many as 70% of patients (Messing and Simon, 1986; Gupta, 1989; Castilla-Guerra et al., 2006). Symptoms with low serum calcium levels depend on the degree of hypocalcemia as well as the rapidity of onset (Castilla-Guerra et al., 2006). However, as with glucose and sodium level variation, the absolute calcium level, seizure threshold, and EEG abnormalities do not correlate well, suggesting that the rate of calcium level decrease may be more important than the absolute value (Goldberg, 1959). The EEG in hypocalcemic patients is characterized by diffuse background slowing with paroxysmal theta/delta activity, as well as focal or generalized spike and spike-wave discharges increased by hyperventilation (Glaser and Levy, 1960). Transient EEG changes in neonates presenting with hypocalcemia-induced seizures include focal, rhythmic, high-voltage, fronto-central epileptiform discharges, often with rapid generalization (Lynch and Rust, 1994; Kossoff et al., 2002). Several cases of hypocalcemia either as the only identifiable or partially contributory cause of NCSE with encephalopathy,

have been described (Vignaendra and Frank, 1977; Nagashima and Kubota, 1981; Thomas et al., 1992; Kline et al., 1998). Similarly, Kumpfel et al. describe a patient with *de novo* focal NCSE who presented with confusion, agitation, hallucinations and impaired language function after rapid correction of iatrogenic hypercalcemia (Kumpfel et al., 2000). EEG showed rhythmic sharp-wave activity predominantly over the right parieto-occipital lobe. Interestingly, NCSE in this patient occurred in the presence of a normal serum calcium level. This case illustrates that the rapidity of change of calcium levels may be of greater epileptogenic potential than absolute levels.

Hypomagnesemia—The main CNS symptoms associated with acute hypomagnesemia are confusion, disorientation, psychosis, mental status depression, and seizures. More than half of patients with low serum magnesium levels have coexisting electrolyte abnormalities, such as hypokalemia, hyponatremia, and hypocalcemia, making it difficult to differentiate these electrolyte abnormalities from the hypomagnesemia, as the cause of encephalopathy (Casaletto, 2010). Hypomagnesemia is usually asymptomatic until serum magnesium levels drop below 1.2 mg/dl, and seizures (usually generalized tonic-clonic) occur when levels fall to less than 1.0 mg/dl (Riggs, 2002; Castilla-Guerra et al., 2006). One case report describes a patient with right-sided hemiparesis and aphasia in the setting of profound hypomagnesemia due to “short gut” syndrome and diarrhea (Leicher et al., 1991). The EEG revealed focal left-sided slowing without epileptiform discharges. Focal symptoms and EEG returned to normal by 6 months.

Other Selected Metabolic Disorders

Wernicke’s encephalopathy—Wernicke’s encephalopathy (WE) is a well-known clinical triad associated with thiamine deficiency, and characterized by cerebellar dysfunction, oculomotor abnormalities, and encephalopathy; however, the complete triad is only present in about 10-20% of patients. Encephalopathy is the most common CNS manifestation and can range from mild confusion to coma. While thiamine deficiency is classically associated with alcohol abuse, numerous other etiologies of malnutrition states have been reported to be associated with thiamine deficiency, including malignancy, acquired immune deficiency syndrome (AIDS), hyperemesis, dialysis, total parenteral nutrition, and gastric bypass (Sechi and Serra, 2007).

EEG changes in WE parallel the severity of the encephalopathy. Diffuse background slowing is followed by low-voltage theta and delta activity predominantly over the fronto-temporal brain regions as the severity of the encephalopathy increases (Frantzen, 1966), at times without EEG background reactivity to external stimuli (Martinez-Barros et al., 1994). Epileptiform activity and seizures in adults are rare, however, in a case series 16/50 patients with clinical manifestations of thiamine deficiency were found to have epileptiform activity on their EEG, or had clinical seizures (Keyser and De Bruijn, 1991). However, 4/16 patients had no history of seizures, but did have epileptiform discharges on their EEG at presentation, suggesting thiamine deficiency as the underlying etiology (Keyser and De Bruijn, 1991). Seizures have been reported in children presenting with infantile thiamine deficiency (Vasconcelos et al., 1999). In 2003, a group of 20 Israeli infants developed various clinical manifestations of thiamine deficiency after being fed a particular brand of soy-based formula devoid of thiamine (Fattal-Valevski et al., 2005). Several years later 7 of these children, then between the ages of 5 and 6 years, were noted to have clinical seizures that were myoclonic, tonic or focal in nature (Fattal-Valevski et al., 2009). Initial EEG showed diffuse background slowing in all but one. Furthermore, focal sharp waves or spikes were observed in 2 cases, and in one patient a right frontal electrographic seizure associated with eye deviation was recorded. Seizures initially resolved with thiamine repletion, however, after a seizure-free period of up to 9 months, virtually all patients developed

recurrent myoclonic, focal motor, or complex-partial seizures (Fattal-Valevski et al., 2009). Follow-up EEGs revealed modified hypsarrhythmia in 3 patients, multifocal epileptiform discharges with and without secondary generalization in another 3 patients, and generalized spike-wave discharges in 1. Only 3 out of 7 children were seizure-free with multiple AEDs, some with the ketogenic diet, and all but one continue to have abnormal EEGs.

Porphyria—Acute intermittent porphyria (AIP) is a relatively rare autosomal dominant disorder caused by deficiency of porphobilinogen deaminase, an important enzyme in the heme synthesis pathway (Anderson et al., 2005). Symptoms of porphyric attacks include colicky abdominal pain, hypertension, tachycardia, peripheral neuropathy, neuropsychiatric manifestations, lethargy, and confusion (Solinas and Vajda, 2008). In the absence of any degree of cognitive impairment, the EEG is usually normal. When presenting with an acute confusional state during a porphyric attack, the EEG initially may show diffuse high-voltage theta and delta slowing, occasionally with focal or multifocal spikes or sharp waves (Goldberg, 1959; Papy et al., 1968; Reichenmiller, 1970; Lipschutz and Reiter, 1974). The prevalence of seizures in the setting of AIP is controversial, with earlier case series estimating that up to 20% of patients present with seizures during a porphyric attack (Goldberg, 1959; Reichenmiller, 1970). More recent studies, however, estimate this number to be much lower. A population-based study of 268 patients registered in the National Porphyria Register in Sweden showed that the life-time prevalence of seizures during an acute porphyric attack was 2.2% in cases with known AIP, and 5.1% in all cases with manifest AIP (Bylesjö et al., 1996). The seizure types described during the porphyric attack with acute mental status changes included complex-partial seizures as well as generalized tonic-clonic seizures (Bylesjö et al., 1996; Engelhardt et al., 2004) (Figure 4). Interestingly, electrolyte abnormalities such as hyponatremia and hypomagnesemia are frequently present during an acute porphyric attack (Tschudy et al., 1975; Anderson et al., 2005). Therefore, it remains unclear whether seizures observed in the setting of porphyric attacks are solely due to the accumulation of neurotoxic compounds as a result of the underlying metabolic defect, or whether concomitant electrolyte abnormalities may play an additional role by lowering seizure threshold (Solinas and Vajda, 2008). Occasionally, seizures may precede the first attack of AIP by years (Birchfield and Cowger, 1966), and the precipitation of subsequent porphyric attacks by AEDs creates a particular challenge in management of these patients (Kaplan and Lewis, 1986). Several cases of PRES in the setting of an acute porphyric attack have been reported, all of which had an encephalopathy with or without seizures (Utz et al., 2001; Celik et al., 2002; Hagemann et al., 2004; Shen et al., 2008; Kang et al., 2010; Kuo et al., 2011; Ni et al., 2011). There are only few reports on EEG changes in PRES related to AIP. EEG recordings in patients with PRES in the setting of acute porphyria show diffuse bilateral theta and delta activity, but no epileptiform discharges (Celik et al., 2002; Kang et al., 2010; Kuo et al., 2011).

Conclusion

The EEG is a relatively inexpensive and easily available diagnostic tool aiding the clinician to identify underlying causes in patients with altered mental status, or encephalopathy. While systematic studies regarding EEG features in metabolic and endocrine encephalopathies are lacking, several distinct EEG features are more commonly seen in some endocrine and metabolic disorders than in others. NCSE for example may be seen in hyperthyroidism, hyper- or hypoglycemia, hyponatremia and hypocalcemia, but not in hypothyroidism, hyper- or hypocortisolism, hypercalcemia, or hypomagnesemia. Similarly, FIRDA has been described in hyperglycemia and hyponatremia, but not in the other metabolic abnormalities, and the presence of PLEDs would suggest hyper- or hypoglycemia, hyponatremia, or hypercalcemia as the underlying etiology. A combination of distinct EEG findings may increase the specificity for the underlying etiology, as summarized in Table 1.

The EEG may aid the clinician by broadening or narrowing the differential diagnosis based on EEG features observed (such as the correlation of the clinical state to the offending electrolyte/hormone disturbance), and may prompt investigation of other metabolic or endocrine abnormalities not routinely investigated. In addition, the EEG is most valuable in identifying NCSE – a significant imitator of encephalopathy and an independently treatable condition. Table 3 provides an overview of endocrine and metabolic abnormalities presenting with NCSE. Finally, the EEG may be useful in determining the severity, course and prognosis of encephalopathy in concert with clinical features and other ancillary tests.

Acknowledgments

R.F. is the recipient of an NIH/National Institute of Neurological Disorders and Stroke R25 training grant. R.S. is supported by the Research Funds of the University of Basel, the Scientific Society Basel, and the Gottfried Julia Bangerter-Rhyner Foundation.

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Figure 1.

The EEG shows periodic sharp waves originating from the left temporo-occipital region with a maximum field at the O1 electrode in a 57 year-old man with alexia without agraphia due to a hyperosmolar, nonketotic state. Serum glucose was 678 mg/dl. Calibration: 1 second between the thick vertical lines, voltage calibration unknown.

Figure 2.

The EEG shows generalized theta activity of 4-6 Hz in an obtunded 58 year-old man with severe encephalopathy due to hypoglycemia with a serum glucose level of 12 mg/dl. Calibration: 1 second per horizontal unit, 70 μ V per vertical unit.

Figure 3.

The EEG shows bioccipital periodic discharges in a patient with new onset cortical blindness due to hypercalcemia-induced posterior circulation vasospasm. Serum calcium was 11.5 mg/dl. Calibration: 1 second per horizontal unit, 70 μ V per vertical unit.

Figure 4.

The EEG shows rhythmic slow activity, most prominent over the left frontal areas, rapidly spreading over both hemispheres in a pregnant 22 year-old woman with status epilepticus due to acute porphyria. Calibration: 1 second/30 mm, 10 μ V/mm.

Table 1
EEG characteristics in metabolic and endocrine disorders

Metabolic Abnormality	PBR	Theta/Delta Activity	Fast Activity	Reactivity	Response to Photic Stimulation	Periodic Delta	Periodic Sharp Waves	FIRDA	PLEDs	TWs	Epileptiform Activity	NCSE
Hyperthyroidism	fast	increased	excessive		prolonged high-voltage					X	X	X
Hypothyroidism	slow	increased (low-voltage)		poor			X			X		
Hypercortisolism	slow	increased	excessive								X	
Hypocortisolism	slow	increased (high-voltage)	decreased							X		
Hyperglycemia	slow	increased (high-voltage)	excessive					X	X		X	X
Hypoglycemia	slow	increased							X		X	X
Hyponatremia	slow	increased (high-voltage)				X		X	X	X	X	X
Hypercalcemia	slow	increased (high-voltage)				X			X	X	X	
Hypocalcemia	slow	increased (high-voltage)										X
Hypomagnesemia	slow	increased (focal)									X	
Thiamine Deficiency	slow	increased (low-voltage; FT max)		poor							X	
Porphyrria	slow	increased (high-voltage; central max)									X	

EEG = electroencephalogram; PBR = posterior background rhythm; FIRDA = frontal intermittent rhythmic delta activity; PLEDs = periodic lateralized epileptiform discharges; TWs = triphasic waves; NCSE = non-convulsive status epilepticus.

Table 2

EEG characteristics in hyponatremia

EEG finding	Reference	Age/Sex	Study Type	Etiology	Neuroimaging	Na levels	Outcome
Background Slowing	Rebelo et al., 1970	65/M	Case Report	hyponatremia after TURP surgery	NR	112 mEq/l	NR
	Reddy et al., 2001	NR	Case Series (5 pts.)	hyponatremia after TURP surgery	NR	131-141 mEq/l	favorable
	Ragoschke-Schumm et al., 2005	16/M	Case Report	desmopressin-induced hyponatremia	MRI brain: "no abnormalities"	120 mEq/l	favorable
Increased Theta/Delta Activity	Okura et al., 1990	44/M	Case Report	water intoxication	NR	117 mEq/l	favorable
Periodic Delta	Nakayama et al., 1999	68/M	Case Report	Rathke's cleft cyst associated with hyponatremia	MRI brain: dumbbell shaped intra- and suprasellar mass with ring-enhancement	115 mEq/l	favorable
FIRDA	Kameda et al., 1995	58/M	Case Report	psychogenic polydipsia	MRI brain: "intrastellar pituitary tumor 10 mm in diameter and slightly deviated to the right side"	Na 137 mEq/l	favorable
	Ragoschke-Schumm et al., 2005	16/M	Case Report	desmopressin-induced hyponatremia	MRI brain: "no abnormalities"	120 mEq/l	favorable
PLEDs	Itoh et al., 1994	50/F	Case Report	NR	CT head: "no organic lesions"	113 mEq/l	favorable
Triphasic Waves	Bahamon-Dussan et al., 1989	NR	Case Report	NR	NR	NR	favorable
	Maruyama et al., 1991	50/M	Case Report	psychogenic polydipsia	CT head: "severely diffuse swelling with largely obliterated sulci and narrowed ventricles"	101 mEq/l	favorable
NCSE	Primavera et al., 1995	53/F	Case Report	water intoxication	CT head: "normal"	90 mEq/l	favorable
	Bartolomei et al., 1998	68/F	Case Report	Addison's disease	CT head: "no lesions"	117 mEq/l	favorable
	Azuma et al., 2008	57/M	Case Report	drug-induced polydipsia	MRI brain: "small lacunars in the left basal ganglia and slight atrophy in the left temporal area"	118 mEq/l	favorable
	Thomas et al., 1992	62/F	Case Report	NR	CT head: "atrophy"	126 mEq/l	favorable
	Ozyurek et al., 2005	5/M	Case Report	NR	MRI brain: PRES	128 mEq/l	favorable
	Lovell et al., 2012	56/M	Case Report	uncontrolled SIADH	CT head: "mild small vessel disease, unchanged from his previous imaging"	116 mEq/l	favorable

EEG = electroencephalogram; Na = sodium; M = male; F = female; NR = not reported; Pts = patients; TURP = transurethral resection of the prostate; MRI = magnetic resonance imaging; FIRDA = frontal intermittent rhythmic delta activity; PLEDs = periodic lateralized epileptiform discharges; NCSE = non-convulsive status epilepticus; CT = computed tomography; SIADH = syndrome of inappropriate antidiuretic hormone secretion; PRES = posterior reversible encephalopathy syndrome

Table 3
Metabolic and endocrine encephalopathies presenting as non-convulsive status epilepticus

Metabolic Disturbance	Reference (single case reports)	Age/Sex	Preexisting Epilepsy	Additional Risk Factors	Metabolic Disturbance and Etiology	Ictal symptoms	Ictal EEG	Neuroimaging	Exam at discharge and follow-up
Hyperthyroidism	Wada et al, 2011	68/F	No	NR	L-Thyroxine administration	short-term memory impairment	continuous 3 to 5 Hz polyspike-and-wave complexes	MRI: normal	No deficit
	Sundaram et al, 1985	17/F	No	mental retardation	L-Thyroxine administration	non-verbal, not following commands, "vacant stare", episodic rapid rhythmic eyelid fluttering and blinking	predominantly occipital continuous bisynchronous spike-and-wave discharges	NR	Baseline exam
Hypонатremia	Azuma et al, 2008	57/M	No	NR	psychogenic polydipsia, Na 118 mEq/L	poor orientation, memory disturbance, confusion, decreased spontaneous speech, bradykinesia	bilateral spike-and - slow wave complexes	MRI: small lacunes in the left basal ganglia and left T atrophy; Interictal SPECT: left F, anterior T hypoperfusion	NR
	Ellis et al, 1978	53/F	No	alcohol abuse, minor head trauma	Na 130 mEq/L	reduced verbal output, incoherent speech, disoriented, bilateral Babinski sign	generalized 1-1.5 Hz multiple spike and wave activity with bifrontal emphasis	CT: mild bi-T cortical atrophy and slight ventricular enlargement	No deficit
	Primavera et al, 1995	53/F	No	drug abuse	psychogenic polydipsia, Na 90 mEq/L	"confusional state with marked slowing of mentation and automatism"	continuous of 3Hz sharp waves intermingled with irregular spike-waves	CT: normal	No deficit
	Thomas et al, 1992	62/F	No	alcohol abuse, medication withdrawal	Na 126 mEq/L	severe clouding of consciousness, myoclonic jerks	continuous generalized irregular 2.5 Hz spike-waves	CT: generalized atrophy	No deficit
	Lovell et al, 2012	56/M	No	NR	uncontrolled SIADH, Na 116 mEq/L	increased tone, waxy catatonias, perseveration, automatisms, fluctuating level of consciousness	continuous sharpened slow wave activity with evolution over the left hemisphere spreading to the right	CT: "mild small vessel disease, unchanged from his previous imaging"	NR
Hypocalcemia	Kumpfel et al, 2000	77/F	No	acute renal failure	rapid correction of hypercalcemia, iCa 3.6 2.2 mmol/L within	confusion, dysphasia, agitation, visual and auditory hallucinations, Balint syndrome, bilateral Babinski sign	rhythmic sharp wave activity with maximum over the right	MRI: subcortical and some cortical FLAIR hyperintensities bilaterally	No deficit

Metabolic Disturbance	Reference (single case reports)	Age/Sex	Preexisting Epilepsy	Additional Risk Factors	Metabolic Disturbance and Etiology	Ictal symptoms	Ictal EEG	Neuroimaging	Exam at discharge and follow-up
Hyperglycemia					hours		parietal-occipital lobe	in the F, P-O lobes	
	Kline et al, 1998	46/M	Yes	NR	idiopathic hypoparathyroidism with non-compliance, iCa 1.02 mmol/L	restlessness, non-verbal, horizontal end gaze nystagmus, left central CN VII palsy, areflexia in the lower extremities	NR, patient returned to baseline shortly after IV Lorazepam administration	CT: normal	No deficit
	Thomas et al, 1992	57/F	No	alcohol abuse, medication withdrawal	iCa 1.78 mmol/L	mild clouding of consciousness	bursts of generalized 2.5 Hz spike waves	CT: normal	No deficit
	Vignaendra et al, 1977	26/F	Yes	NR	iCa 2.60 mmol/L	reduced verbal output, "dazed", bilateral Babinski sign	rhythmic, generalized, bilaterally synchronous sharp and slow waves at 2.5 Hz	NR	No deficit
	Nagashima et al, 1981	31/M	No	NR	serum calcium 5.9 mg/dl	loss of consciousness and prolonged period of unresponsiveness without tonic or clonic movements	continuous bisynchronous 2.5 Hz sharp and slow waves with little or no response to physiologic stimulation	CT: symmetric hyperdensity in the bilateral putamen and head of the caudate without enhancement	No deficit
	Manford et al, 1995	74/M	No	NR	uncontrolled DM, serum glucose 697 mg/dl	aphasia, apraxia, gait ataxia, nystagmus	10 to 12 Hz seizure discharges, maximally over the left mid to posteriotemporal area	CT: generalized atrophy; SPECT: reduced uptake in the left superior T and inferior F gyri	No deficit
	Kutluay et al, 2007	57/M	No	NR	uncontrolled DM, serum glucose 678 mg/dl	alexia without agraphia	periodic sharp waves followed by rhythmic 8 to 9 Hz left temporo-occipital epileptiform discharges	MRI: FLAIR hyperintensities in the left T-O junction involving the middle O, middle T gyri	No deficit
	Pro et al, 2011	52/M	No	NR	uncontrolled DM, serum glucose 350 mg/dl	incoherent speech, inability to repeat	left temporal 14-15 Hz fast activity, followed by high voltage irregular sharp and slow waves	MRI: normal	No deficit

Metabolic Disturbance	Reference (single case reports)	Age/ Sex	Preexisting Epilepsy	Additional Risk Factors	Metabolic Disturbance and Etiology	Ictal symptoms	Ictal EEG	Neuroimaging	Exam at discharge and follow-up
Hypoglycemia	Dion et al, 2004	37/F, 44/M, 55/F	No	NR	insulinoma, serum glucose range 16 to 31 mg/dl	Confused speech and behavior, agitation, gait ataxia, unresponsiveness, paranoia	diffuse ictal slow waves	MRI: normal	No deficit
	Wang et al, 2008	53/F	No	NR	insulinoma, serum glucose 27 mg/dl	stereotyped behavior, unresponsiveness, confusion	build-up of theta and delta, followed by sporadic spikes and sharp waves as well as slowing	MRI: normal	No deficit

EEG = electroencephalogram; M = male; F = female; L-Thyroxine = Levothyroxine; Hz = Hertz; MRI = magnetic resonance imaging; NR = not reported; Na = Sodium; T = temporal; F = frontal; P = parietal; O = occipital; SPECT = single photon emission computed tomography; CT = computed tomography; SIADH = syndrome of inappropriate antidiuretic hormone secretion; FLAIR = fluid attenuated inversion recovery; CN = cranial nerve; IV = intravenous; iCa = ionized calcium; DM = diabetes mellitus