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Metabolic Encephalopathy: Behind the Name

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Abstract
Metabolic encephalopathy may be the most common diagnosis in consultative acute neurology. The origin of this term is not generally known but can be traced back. The term replaced more commonly used designations such as organic or functional. The term metabolic encephalopathy was originally linked to organ dysfunction but subsequently became more imprecise. When it expanded to include a large number of diseases, it evolved to "metabolic neuronal dysfunction" and soon could not be distinguished from "quiet delirium" and other designations. This vignette summarizes why the terminology has confused more than clarified but also why it will likely stay in the neurologist's vernacular.

Keywords Metabolism · Encephalopathy · Metabolic neuronal dysfunction · Toxic · Terminology · Delirium

Introduction

Maybe it is Some Metabolic Sort of Thing

The above statement was a resident's explanation for a patient's elusive presentation called—for convenience—an toxic-metabolic encephalopathy. I always wondered about the origin of the undescriptive term "metabolic encephalopathy," which has been applied extensively to patients seen in consultation on wards and intensive care units (ICUs), particularly if they are inattentive, disoriented, or even agitated. "Toxic" is often added to the description.

Why do we use this term to denote abnormal behavior and cognition? According to the Oxford Dictionary, metabolism is defined as *the chemical processes that occur within a living organism in order to maintain life*. Encephalopathy is defined as *a disease in which the functioning of the brain is affected by some agent or condition.* I will discuss the origin and historical evolution of the term "metabolic encephalopathy" and how it likely became part of the neurologist's vocabulary. Medical terminology is full of place markers. Some catch on and others keep trying.

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Terminology

The specialty neurology is known for a large number of terms to delineate a confused patient. Liston collected many terms in a list that included "acute brain failure and acute brain insufficiency," subacute befuddlement, dysergastic reaction, pseudo-senility, toxic delirious reaction, toxic encephalopathy, toxic psychosis, and the ubiquitous "altered mental status"—likely tongue in cheek and with the implied purpose to jettison most of them [1]. "Clouding of consciousness" was used in the first version of DSM–III and then disappeared. Quiet delirium is the new term but many neurologists would not want to equate a delirious patient with quietness [2].

Neurologists understand the difficulty of ascertaining what is going on in the brain and with the patient but, for many years, they had the tendency to call it all "multifactorial metabolic encephalopathy" and then subsequently listed the abnormalities that comprised the patient's critical illness. Metabolic encephalopathy may mimic structural lesions, and organ dysfunction can be associated with poor clearance of medication. Pharmacogenomics and pharmacogenetics in critically ill patients is an emerging field and may show poor metabolism may be a major factor.

Generally, how illness affects neuronal circuitry is not understood [3–6]. Neurologists over many years have labeled patients with abnormal response: somnolent, encephalopathic, drowsy, disoriented, and, when agitated, delirious. Delirium often has been diagnosed when

confusion accompanies autonomic symptoms such as profuse sweating, muscle twitching, fidgety movements, and even more focused movements such as removing lines and catheters. Some have suggested discarding encephalopathy altogether and substituting the term "hypoactive delirium" for less attentive patients with paucity of movement as opposed to "hyperactive delirium," a condition characterized by increased attention, agility, and exaggerated response to a simple stimulus [7]. Still, one can also easily imagine hypoactive delirium harboring a CNS infection, nonconvulsive status epilepticus, a new metabolic derangement such as hyperammonemia, or a major side effect of an administered drug. How about a patient who is cortically blind from cerebral infarctions?

The origin of the term metabolic encephalopathy likely comes from Glaser [8], who interpreted an article on the pathological physiology of cerebral dysfunction in 1958 [9] by Fazekas who was a neurologist at the New England Medical Center Hospital at Tufts University School of Medicine. In 1962, he and Alman wrote a book in which coma was attributed to oxygen insufficiency, substrate insufficiency, enzymatic disturbances, and multiple etiologies including infections, seizures, and space-occupying lesions [10]—lesions that later became better described by Plum and Posner) [11]. Glaser titled the article "Metabolic Encephalopathy in Hepatic, Renal, and Pulmonary Disorders" [8]. Glaser defined a metabolic encephalopathy as "manifested clinically by acute and chronic disturbances of intellectual performance and motor and sensory activities ranging from mild confusional states to coma." He defined metabolic encephalopathy as the result of insufficiency of substrate, oxygen, or both with interference of cerebral enzymatic activity, transport of metabolites such as amino acid and electrolytes into a nerve cell, and oxidative phosphorylation by effects of unstimulated neuronal respiratory processes [8]. He described portosystemic encephalopathy as a metabolic encephalopathy with "lack of essential metabolites" such as nucleosides, serotonin precursors, and retention of bilirubin and porphyrin, largely taking material from Sherlock's work [12].

More significantly, in 1966, in their classic monograph *The Diagnosis of Stupor and Coma,* Plum and Posner categorized all abnormalities as metabolic [11], further distinguishing between primary and secondary metabolic encephalopathies. The book broadly classified the metabolic causes and included meningitis, subarachnoid hemorrhage, and cerebral vasculitis as metabolic encephalopathies. It cemented the distinction between "structural" and "toxic-metabolic" causes of coma, and that distinction has remained a clinical guide for neurologists. The book also produced a table of toxic and metabolic coma based on changes in respiration (hypoventilation or hyperventilation). Table 6 in their book is illustrative, showing the categorization of virtually all lesions not associated with cerebral edema or ischemic or hemorrhagic injury to neuronal structure (Fig. 1). Plum and Posner introduced a deductive thinking process based on structural versus non-structural and used the tentorium as a dividing structure. They classified comatose states in supratentorial lesions causing coma, subtentorial lesions causing coma, and metabolic brain diseases causing coma (in later editions, psychogenic unresponsiveness was added). "This final category of comatose states is caused by diffuse failure of neuronal metabolism." Terms such as toxic psychosis, delirium, and acute confusional states were grouped under secondary metabolic encephalopathies. Plum and Posner defended the inclusion of concussion, postictal coma, coma due to meningitis, and coma due to subarachnoid hemorrhage as metabolic. They argued that lack of consciousness is due to "widespread and often reversible interference with brain metabolism," and these disorders "resemble other forms of metabolic coma" and differ from the other lesions (masses and destructive lesions).

Additional components of metabolic encephalopathy examined by Plum and Posner included alertness, orientation and grasp, cognition and attention, memory, affect and perception, respiratory effect, pupils (preserved light reflex at all times), ocular motility (roving and conjugate eye movements),tremor, asterixes, multifocal myoclonus, and a "diffusely, nonfocally slow" EEG.

The impact of this classification on neurologic practice has been substantial and cemented in neurologic diagnostic algorithms that help to categorize patients not fully aware of their surroundings. Despite the lack of a better term, we now know that many patients with so-called toxic-metabolic encephalopathy might have other diagnoses. It has become clear over the years that posterior reverse encephalopathy syndrome (PRES) is a major manifestation of acute renal disease and end-stage renal disease. PRES can be expected with a sudden surge of hypertension, autoimmune diseases, and evolving gram-positive sepsis. PRES is mostly related to major flare-ups of hypertension or new presentation of severe hypertension, but this complication relationship can also occur without hypertension. Moreover, not emphasized in many textbooks and chapters, an overwhelming proportion of patients in ICUs are unable to metabolize drugs, either due to vital organ dysfunction due to drug-to-drug interactions or yet to be determined genetic factors [13, 14].

Organ failure-associated encephalopathies comprise a sprawling number of disorders, and neurologists appreciate the difficulty of determining the actual etiology. I suspect multifactorial metabolic encephalopathy is the most commonly used term by neurologists, but it tells us nothing and is a sort of physiologic neuronal dysfunction in search of facts and perhaps a name.

Table 6. Metabolic causes of stupor and coma

I. Stupor or Coma Arising from Intrinsic Diseases of the Neurons or Neuroglial Cells (Primary Metabolic Encephalopathy)
- A. Gray Matter Diseases:
  - Jakob-Creutzfeldt disease
  - Pick's disease[259]
  - Alzheimer's disease and senile dementia[200, 328]
  - Huntington's chorea[27]
  - Progressive myoclonic epilepsy[272]
  - Lipid storage diseases[282, 307]
- B. White Matter Diseases:
  - Schilder's disease
  - Marchiafava-Bignami disease
  - The leukodystrophies[68, 142]

II. Stupor or Coma Arising from Diseases Extrinsic to Neurons and Glia (Secondary Metabolic Encephalopathy)
- A. Deprivation of Oxygen, Substrate, or Metabolic Cofactors
  1. Hypoxia (interference with oxygen supply to the entire brain—cerebral blood flow normal)
     - a. Decreased oxygen tensions and content of blood
       - Pulmonary disease
       - Alveolar hypoventilation
       - Decreased atmospheric oxygen tension
     - b. Decreased oxygen content of blood—normal tension
       - Anemia
       - Carbon monoxide poisoning
       - Methemoglobinemia
     - c. Normal oxygen content and tension of blood—brain oxygen needs increased
       - Seizures and postictal states
  2. Ischemia (diffuse or widespread multifocal interference with blood supply to brain)
     - a. Decreased cerebral blood flow resulting from decreased cardiac output
       - Stokes-Adams; cardiac arrest; cardiac arrhythmias
       - Myocardial infarction
       - Congestive heart failure
       - Aortic stenosis
     - b. Decreased cerebral blood flow resulting from decreased peripheral resistance in systemic circulation
       - Syncope: orthostatic, vasovagal
       - Carotid sinus hypersensitivity
       - Low blood volume
     - c. Decreased CBF due to increased vascular resistance
       - Hypertensive encephalopathy
       - Hyperventilation syndrome
       - Increased blood viscosity (polycythemia)
  3. Hypoglycemia
     - Resulting from exogenous insulin
     - Spontaneous (endogenous insulin, liver disease, etc.)
  4. Cofactor deficiency
     - Thiamine (Wernicke's encephalopathy)
     - Niacin
     - Pyridoxine
     - B_1
- B. Diseases of Organs Other Than Brain
  1. Diseases of nonendocrine organs
     - Liver (hepatic coma)
     - Kidney (uremic coma)
     - Lung (CO_2 narcosis)
  2. Hyperfunction and/or hypofunction of endocrine organs
     - Pituitary[254]
     - Thyroid (myxedema-thyrotoxicosis)
     - Parathyroid (hyperparathyroidism and hypoparathyroidism)
     - Adrenal (Addison's disease, Cushing's disease, pheochromocytoma)
     - Pancreas (diabetes, hypoglycemia)
  3. Other systemic diseases:
     - Cancer
     - Porphyria[20, 229]
- C. Exogenous Poisons
  1. Sedative drugs
     - Barbiturates
     - Nonbarbiturate hypnotics
     - Tranquilizers
     - Bromides
     - Ethanol
     - Anticholinergics
     - Opiates
  2. Acid poisons or poisons with acidic breakdown products
     - Paraldehyde
     - Methyl alcohol
     - Ethylene glycol
  3. Enzyme inhibitors
     - Heavy metals[4, 145]
     - Organic phosphates
     - Cyanide[27]
     - Salicylates
- D. Abnormalities of Ionic or Acid-Base Environment of CNS
  1. Water and sodium (hypernatremia and hyponatremia)
  2. Acidosis (metabolic and respiratory)
  3. Alkalosis (metabolic and respiratory)
  4. Potassium (hyperkalemia and hypokalemia)
  5. Magnesium (hypermagnesemia and hypomagnesemia)[145]
  6. Calcium (hypercalcemia and hypocalcemia)
- E. Diseases Producing Toxins or Enzyme Inhibition in CNS
  - Meningitis
  - Encephalitis
  - Subarachnoid hemorrhage
- F. Traumatic Neuronal Dysfunction without Structural Change (Concussion)

◀**Fig. 1** Classification of metabolic causes of stupor and coma (Table From Plum and Posner, The diagnosis of stupor and coma, 1st ed. [11], reprinted Copyright (1966), with permission from Elsevier.)

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