TOXIC DELIRIUM WITH SPECIAL REFERENCE TO ANTICHOLINERGICS

A THESIS

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Presented by

OUSSAMA SELIM ABOU-ZEID

M.Sc. Pediatrics

Under the supervision of

PROF. DR. MOUSTAFA ABD EL LATIF KAMEL

Professor of Forensic Medicine and Clinical Toxicology

Ain Shams University

PROF. DR. HANY AHMED GAMAL EL DIN

Professor of Forensic Medicine and Clinical Toxicology

Ain Shams University

DR. HODA SALAH OSMAN

Lecturer of Forensic Medicine and Clinical Toxicology

Ain Shams University

Faculty of Medicine

Ain Shams University

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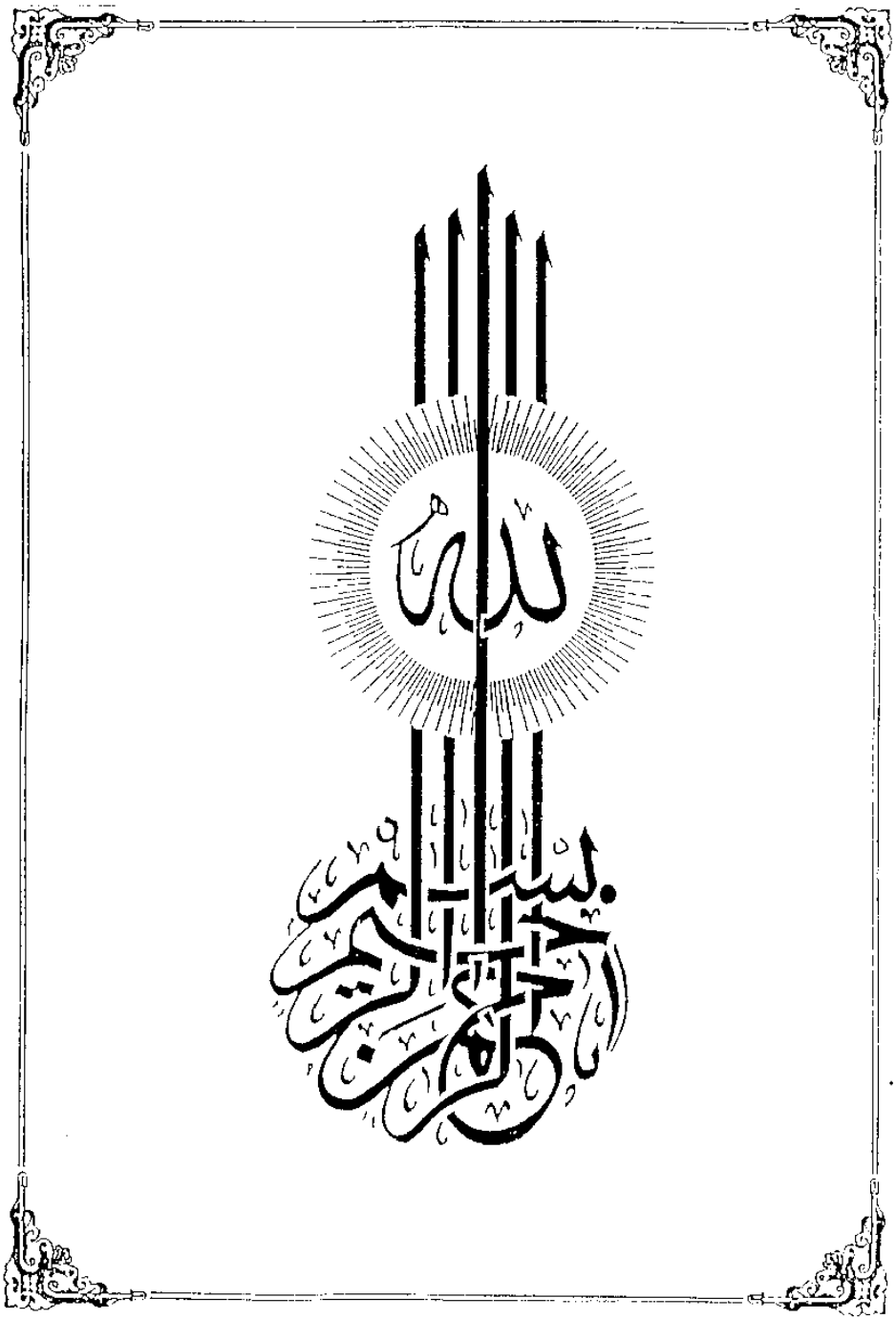

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INTRODUCTION

Semantic Origin

Synonym of delirium is hysteria, frenzy. In Latin delirium is delira or rave, be crazy; literally: go out of the furrow (*Barnhart and Barnhart,* 1990).

It is a temporary disorder of the mind that occurs during fevers, insanity, drunkenness, or a drugged state. It is characterized by restlessness, excitement, strange ideas, and wild talk (*Berkow et al.,* 1982).

Delirium tremens is a mental and nervous disorder accompanied by violent tremblings and terrifying hallucinations, usually caused by prolonged and excessive drinking of alcoholic liquor, and its withdrawal with associated malnutrition. Latin delirium tremens is trembling delirium (*Barnhart and Barnhart,* 1990).

Medical Definition

Syndrome of delirium is an acute or subacute reduction in awareness, attention, and perception (clouding of consciousness) usually fluctuating or transient in nature (*Wyngaarden and Smith,* 1988), and

accompanied by a dream-like state, reversal of sleep, wake cycles, and sometimes prolonged insomnia or excessive day-time sleep (*Andreoli et al.*, 1986). It may occur at any age (*Berkow et al.*, 1982).

The term is sometimes used synonymously with acute reaction or brain syndrome or acute confusional state (*Weatherall et al.*, 1984). To a greater or lesser extent, the terms: Symptomatic psychosis, toxic psychosis, infective-exhaustive psychosis, and drug, traumatic, or febrile delirium, all have reference to the syndrome of delirium. Each of these terms conveys the idea of an acute and transient (reversible) confusional state, occurring in a particular clinical setting, and carrying a serious prognosis, by virtue of adding its burden to an already serious medical illness (*Petersdorf and Fauci*, 1986).

The term delirium or acute toxic psychosis is employed for the more agitated and severely disoriented, hallucinatory - delusional forms of metabolic encephalopathy. Quieter, less severe disturbances have been termed acute or subacute confusional states (*Wyngaarden et al.*, 1992). Implicit in the definition are certain non-medical connotations of the term agitation, excitement, vivid dreams, and creations of imagination (*Petersdorf and Fauci*, 1986).

The American Psychiatric Association's Diagnostic Manual, applies the term delirium to all examples of acquired confusion, agitation, disorientation, or hallucinations occurring in the setting of structural or known neurochemical brain disease (*Wyngaarden et al.*, 1992).

Physiologic Mechanisms of Delirium

In a trial of analysis of several conditions conductive to delirium, *Petersdorf and Fauci* (1986) suggested three different physiologic mechanisms: First, the withdrawal of alcohol, barbiturate, or other sedative-hypnotic drugs, following a period of chronic intoxication, is the most common cause of delirium. These drugs have a strong depressant effect on certain areas of the central nervous system; presumably the release and overactivity of these parts, after withdrawal of the drug, are the basis of the delirium. Second, in the case of bacterial infections, toxic encephalopathies, or drug induced delirium such as occurs with atropine or scopolamine, the delirious state probably results from the direct action of the toxin, toxic biproducts, or chemical agents on these same parts of the brain. Third, destructive lesions, such as those of the temporal lobes in trauma or Herpes simplex encephalitis, may cause delirium by disturbing the function of these particular areas.

Review of Literature

ETIOLOGY OF DELIRIUM

Delirium may occur with a wide range of clinical conditions, and it is a common problem in medical and surgical wards (*Berkow et al.*, 1982). Clinical conditions causing delirium can broadly fall into 2 groups: metabolic disorders and structural lesions.

Clouding of consciousness implies disturbance of function of the reticular activating system, and because of its polysynaptic nature, this region of the brain stem and diencephalon is susceptible to the action of many abnormal metabolites and toxins. So delirium reaction may occur due to toxic causes, and can accompany febrile conditions, liver or renal failure, myxedema, or either hypo- or hyperglycemia, or occur in association with thiamine or nicotinic acid deficiencies, or in the course of cardiac or pulmonary failure (*Harwood-Nuss et al.*, 1991).

Structural lesions can lead to delirium states. These include meningitis and encephalitis; cerebral neoplasms when multiple or causing an intracranial pressure rise and shift; cerebral abscess; large subdural hematomas; head injury; or cerebral infarction or bleeding. The brain is displaced, and there is stretching and spasm of the perforating branches originating from the basilar, superior cerebellar, posterior communi-

cating, and posterior cerebral arteries that supply the central region of the brain-stem and diencephalon, including the reticular activating system. Necessarily, this interference with blood supply also leads to disturbed cerebral cortical function (*Berkow et al.*, 1982).

In hospital and emergency room prescribed medications to patients are common causes of delirium (Table A). A thorough medication history and review of the patient's medication records are essential. The doctor's order sheets can be misleading, since drugs may have been ordered but not given. Correlations of changes in behavior with medication administration or discontinuation can be helpful in sorting through a difficult case (*Civetta et al.*, 1988).

Table (A): Drugs causing delirium (after *Civetta et al.*, 1988).

Analgesics
- Meperidine (Normeperidine)
- Opiates
- Pentazocine
- Salicylates

Antibiotics
- Acyclovir (antiviral)
- Aminoglycosides
- Amodiaquine
- Amphotericin B (antifungal)
- Cephalosporins
- Chloramphenicol
- Chloroquine (antimalarial)
- Ethambutol
- Gentamicin
- Interferon (antiviral)
- Isoniazid
- Rifampin
- Sulfonamides
- Tetracyclines
- Ticarcillin
- Vancomycin

Anticholinergics
- Antihistamines
- Chlorpheniramine (Ornade, Teldrine)
- *Antiparkinson drugs*
- Benzotropine (Cogentin)
- Biperidin (Akineton)
- Antispasmodics
- Belladonna alkaloids
- Diphenhydramine (Benadryl)
- Phenothiazines (especially Thioridizide)
- Promethazine (Phenergan)
- Tricyclic antidepressants (especially Amitriptyline)
- Trihexyphenidyl (Artane, Pipanol, Tremin)

Anticonvulsants
- Phenobarbital
- Phenytoin (Dilantin)
- Sodium valproate (Depakene)

Anti-inflammatory
- ACT
- Corticosteroids
- Ibuprofen (Motrin, Advil)
- Indomethacin (Indocin)
- Naproxen (Naprosyn)
- Phenylbutazone (Butazolidin, Azolid)
- Steroids

Antineoplastics
- Aminoglutethimide
- DTIC
- 5-fluorouracil
- Hexamethylenamine
- L-asparaginase
- Methotrexate (high dose)
- Tamoxifen
- Vinblastine
- Vincristine

Antiparkinsons
- Amantadine (Symmetrel)
- Bromocriptine
- Carbidopa (Sinemet)
- Levodopa (Larodopa)

Cardiac
- Beta-blockers
- Captopril
- Clonidine (Catapres)
- Digitalis (Digoxin, Lanox)
- Disopyramide (Norpace)
- Lidocaine (Xylocaine)
- Mexilitene
- Methyldopa (Aldomet)
- Quinidine (Quinidine, Quiaglute, Duraquine)
- Procainamide (Pronestyl)
- Tocainide

Drug Withdrawal
- Alcohol
- Barbiturates
- Benzodiazepines

Sedative-Hypnotics
- Barbiturates (Miltown, Equanil)
- Benzodiazepines
- Glutethimide

Sympathomimetics
- Aminophylline
- Amphetamines
- Cocaine
- Ephedrine
- Phenylephrine
- Phenylpropanolamine
- Theophylline

Miscellaneous Drugs
- Baclolen
- Bromides
- Chlorpropamide (Diabinese)
- Cimetidine (Tagamet)
- Disulfiram (Antabuse)
- Ergotamines
- Lithium
- Metrizamide (Amipaque)
- Metronidazole (Flagyl)
- Phenelzine
- Podophyllin (by absorption)
- Procarbazine
- Propylthiouracil
- Quinacrine
- Ranitidine
- Timolol ophthalmic

TOXIC CAUSES OF DELIRIUM

Toxic delirium is generally associated with substance abuse disorders, suicidal or accidental drug overdoses, and idiosyncratic reactions to drugs. The pathogenic mechanism depends on the pharmacologic action of the drug. Clinically toxic delirium can be classified into three categories: dose related as with anticholinergics, tricyclic antidepressants, phenothiazines or monamine oxidase inhibitors; side effect or idiosyncratic as with mepiridine, procainamide, hydantoins or cimitidine (*Okasha,* 1988). Delirium may also be a feature of drug withdrawal, the delirium tremens of ethanol being the best known, but withdrawal from chronic use of many pharmacologic agents, such as benzodiazepines, ethchlorvynol, barbiturates, meprobamate, and neuroleptics, also may be considered (*Wilson and Gallagher,* 1988; *Sandoval and Palermo-Neto,* 1986).

Delirium in Hospitalized and Anesthetized Patients

Delirium in hospitalized patients is most closely associated with factors already present on admission such as prior cognitive impairment, advanced age, and fracture. In the hospital, the use of neuroleptics and

narcotics, and the presence of infection are less strongly associated with delirium (*Schor et al.*, 1992).

Post-anesthetic delirium is a type of post-operative emotional response occurring immediately after emergence from general anesthesia, associated with excitement and confusion. The alternative terms: emergence delirium or post-anesthetic excitement are frequently used. The term post-operative psychosis is used interchangeably, but more frequently refers to those conditions occurring after a lucid interval of 24 to 48 hours (*Olympio,* 1991).

Delirium in hospitalized and in anesthetized patients may arise from a variety of disturbances, with drug reactions, hypoxemia, or reaction to pain being common, or it may arise from psychological causes (*Olympio,* 1991).

Geriatric patients are more sensitive than their youthful counterparts to the central nervous system side effects of drugs specially delirium or dementia (*Bernick and Stern,* 1985).

Drug Combination and Delirium

Patients taking multiple medications may be at increased risk for side effects from psychotropic drugs, most of which have anticholinergic

effects (*Tune et al.*, 1992b). Overmedication with a number of different drugs is common, for this reason, the use of all non-essential drugs in confused or demented patients should be stopped. Anticholinergic actions of non-prescribing agents as hypnotics, antihistaminics, antispasmodics, antiparkinsonian, antipsychotics, and antidepressants can precipitate or aggravate confusion among people with minimal early dementia (*Bernick and Stern*, 1985).

Examples of Drugs Causing Delirium

Sympathomimetics

1. **Amphetamines**: e.g. Methamphetamines, Phenmetrazine (Preludin) and Mephentermine (Wyamine). On physical examination patient shows dry mouth, diaphoresis, tachycardia, hypertension, hyperactivity, active bowel sounds, reactive mydriasis, hyperthermia, headache, dyskinesia, difficulty on micturition, subarachnoid hemorrhage and coma. Psychiatric examination shows agitation, confusion, delirium, auditory and visual hallucinations, paranoia and suicidal and homicidal ideation (*Derlet and Heischober*, 1990). Ischemic stroke was described after methamphetamine nasal inhalation (*Rothrock et al.*, 1988). Cerebral infarction was associated with chronic oral therapeutic use of methyl phenidate in a 12-year old