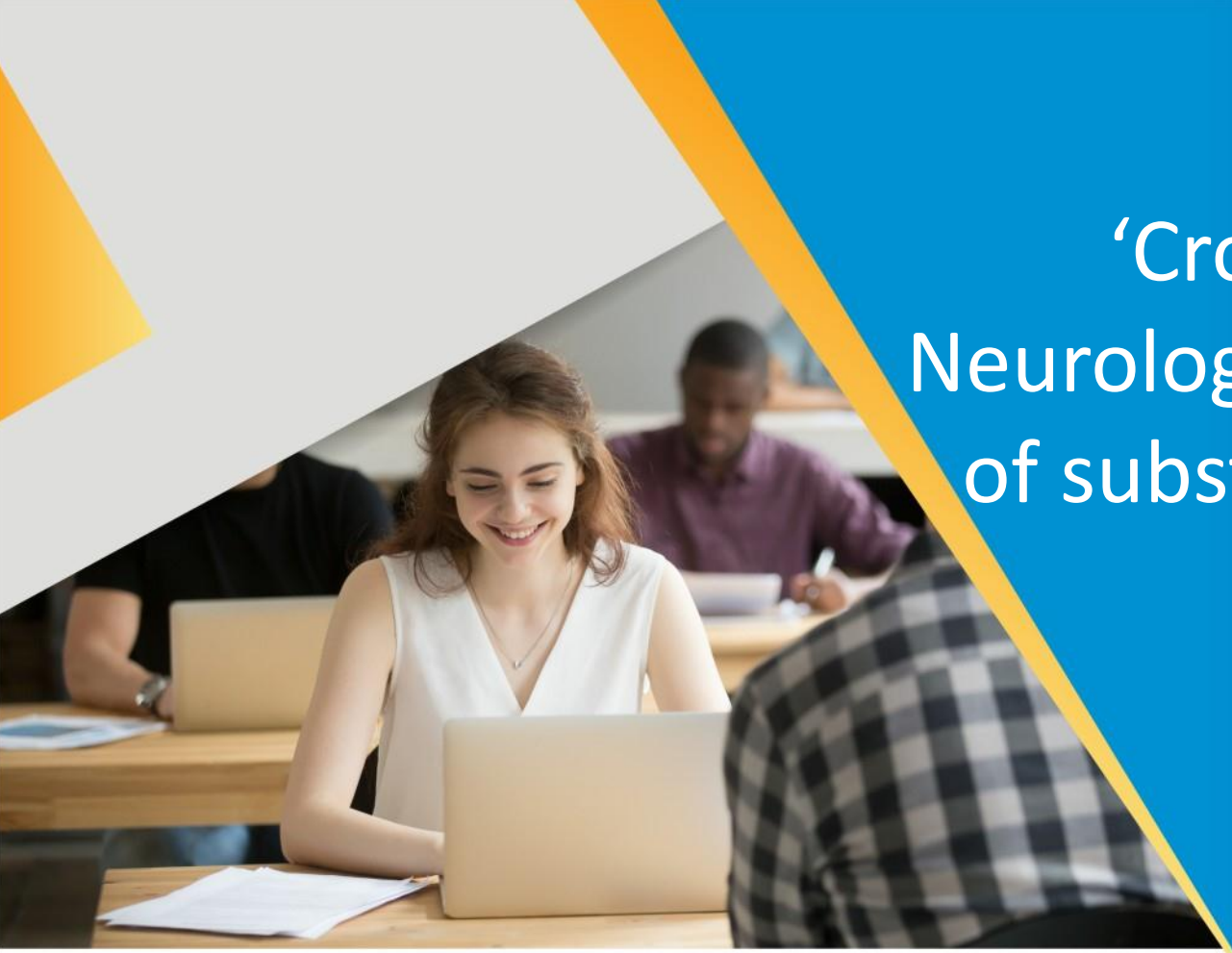

‘Crooked brain’ Neurological aspects of substance abuse

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I will talk of neurological aspects of

- Alcohol
- Other substances

Alcohol

Definition of alcoholism

- If a person drinks on a regular basis for many years
  - Men: 6 standard drinks a day >8 years
  - Women: 3 drinks a day
- Over a short period of time, if the drinking is aggressive enough (binge drinking)
  - Men: >7 standard drinks
  - Women: >5 standard drinks on any single occasion

Standard drink

- Beer: 330 ml
- Wine: 150 ml
- ‘Hard drinks’: 30 ml
- Arrack: 1/3 sachet

Neurological complications of alcoholism

Effects of alcohol

- Acute effects
  - Intoxication
  - Seizures
  - Falls/accidents
- Methanol toxicity
- Marchiafava Bignami disease
- Withdrawal effect
  - Withdrawal seizures
  - Delirium tremons
- Chronic effects
  - Dementia
  - Frontal lobe syndrome
  - Cerebellar syndrome
  - Peripheral neuropathy
  - Myopathy
- Fetal alcohol syndrome

Effects of alcohol

- Secondary effects
  - Thiamine deficiency: Wernicke Korsak off syndrome
  - Nutritional deficiency myelopathy
  - Central pontine myelinosis
  - Hepatic encephalopathy
  - Ambylopia
  - Increased risk of strokes

Acute intoxication

- Alcohol is CNS depressant
- The amount of alcohol consumed to become stuporous will vary from person to person
- Many other disorders can be missed for alcohol intoxication
  - Traumatic brain injury
  - WKS
  - Hypoglycemia

Methanol toxicity

- Used as industrial solvents, carburettor fluid, antifreeze fuels, and in many other products
- Used as cheap adulterant with alcohol
- Presents with
  - Encephalopathy
  - Shock
  - Lactic acidosis
  - Blindness
- Antidote: ethanol, fomepizole

Withdrawal syndrome

- Neurological complications
  - Seizures
    - May not require long term treatment
  - Tremors
  - Autonomic dysfunction
    - Clonidine may be useful
  - Rhabdomyolysis

Effect of alcoholism

- Problem solving
- Attention
- Short-term memory
- Visuo-spatial ability
- Balance and postural stability

Effect of alcoholism

- Impaired judgment
- Blunted affect
- Poor insight
- Social withdrawal
- Reduced motivation
- Distractibility
- Cognitive rigidity
- Inattention
- Perseveration

Executive Functions

Effect of alcoholism

- Poor sense of direction
- Impaired constructional ability
- Impaired spatial placement
- Impaired drawing ability

} Visuo-spastial abilities

Effect of alcoholism

- Impaired timing
- Impaired tracking
- Impaired balance
- Impaired gait
- Increased falls

Motor control

Fetal alcohol syndrome

- Features
  - Abnormal cognition and behavior
  - Microcephaly
  - Prenatal and postnatal growth reduction
  - Characteristic facies

Disabilities in fetal alcohol syndrome

Lower IQ	Memory Problems
1. Impaired ability in reading, spelling, and arithmetic 2. Lower level of adaptive functioning; more significantly impaired than IQ	1. Multiplication 2. Time sequencing
Sensory Integration Issues	**Information Processing Problems**
1. Overly sensitive to sensory input 2. Upset by bright lights or loud noises; by tags in shirts or seams in socks; certain textures of food 3. Have problems sensing where their body is in space (i.e., clumsy)	1. Do not complete tasks or chores -appear to be oppositional 2. Have trouble determining what to do in a given situation 3. Do not ask questions because they want to fit in

Peripheral neuropathy

- Neuropathy is common in chronic alcoholic persons
- Features:
  - Parasthesias/pain/tingling in legs>arms
  - Imbalance while walking
  - Motor power usually preserved
- Caused with toxic effect of alcohol and additional nutritional deficiencies

Marchiafava Bignami syndrome

- Extremely rare condition
  - Almost exclusively occurs in male alcoholics
  - Originally described in Italian red wine drinkers
- Clinical picture
  - Acute form, with seizures, severe neurological disturbances and disorders of consciousness
  - Chronic form with progressive dementia or interhemispheric disconnection syndrome

Marchiafava Bignami syndrome

- Diagnosis is with MRI brain
  - It shows diffuse swelling of the corpus callosum (oedema) and demyelination with subsequent atrophy
- Pathogenesis: unknown
- Outcome: Recovery with good functional outcome can occur

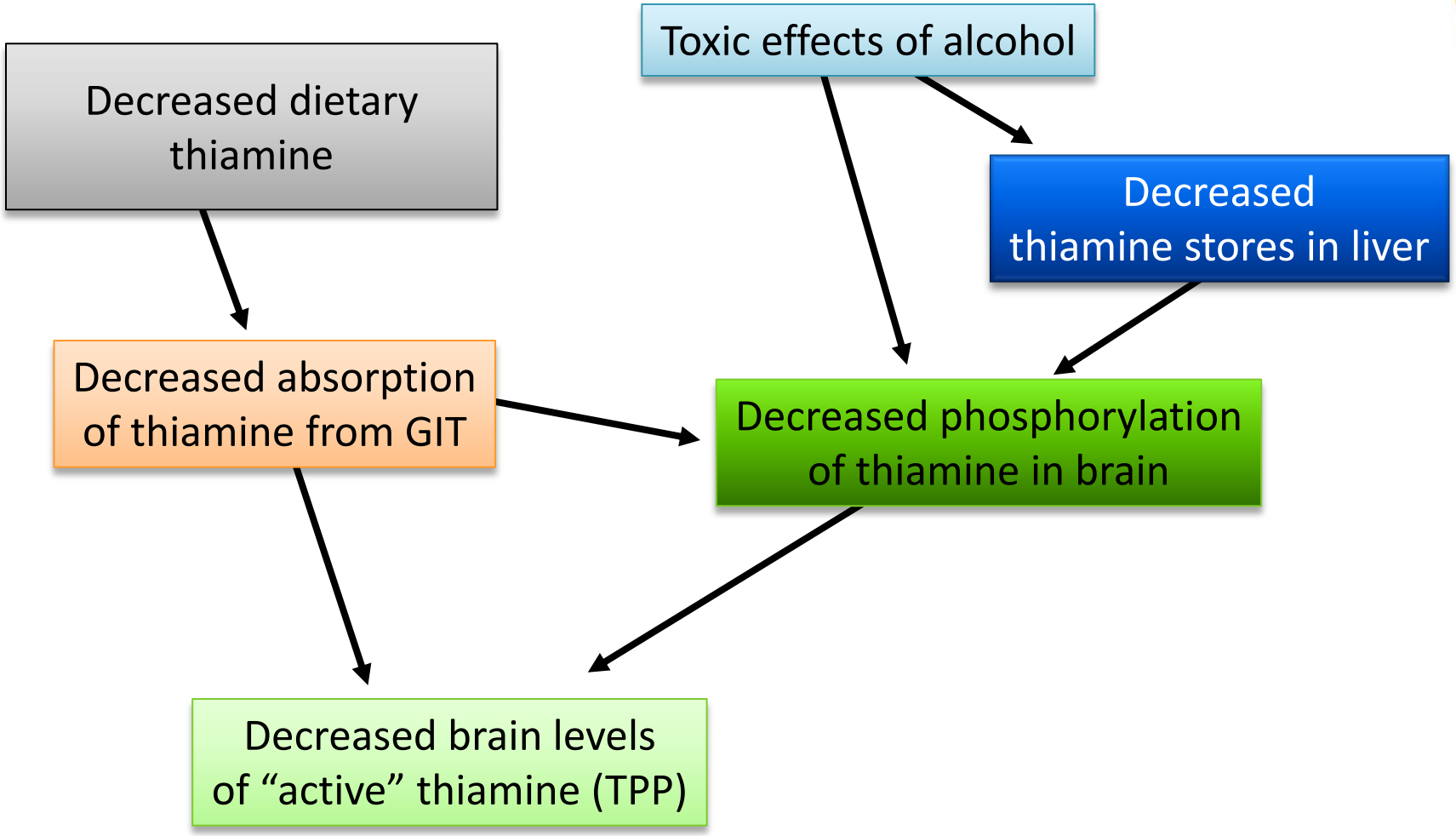
Wernicke's encephalopathy

- The disorder is called Wernicke's encephalopathy in the acute phase, which can progress to Korsakoff's psychosis
  - It is sometimes referred to as Wernicke-Korsakoff syndrome (WKS)
- Caused by thaimine (vitamin B1) deficiency

WKS: 'other' causes

- Hyperemesis of pregnancy
- Systemic malignancy
- GI surgery
- Hemodialysis or peritoneal dialysis
- Prolonged IV feeding
- Anorexia nervosa
- Refeeding after prolonged starvation
- AIDS

Interactions between alcohol and B1



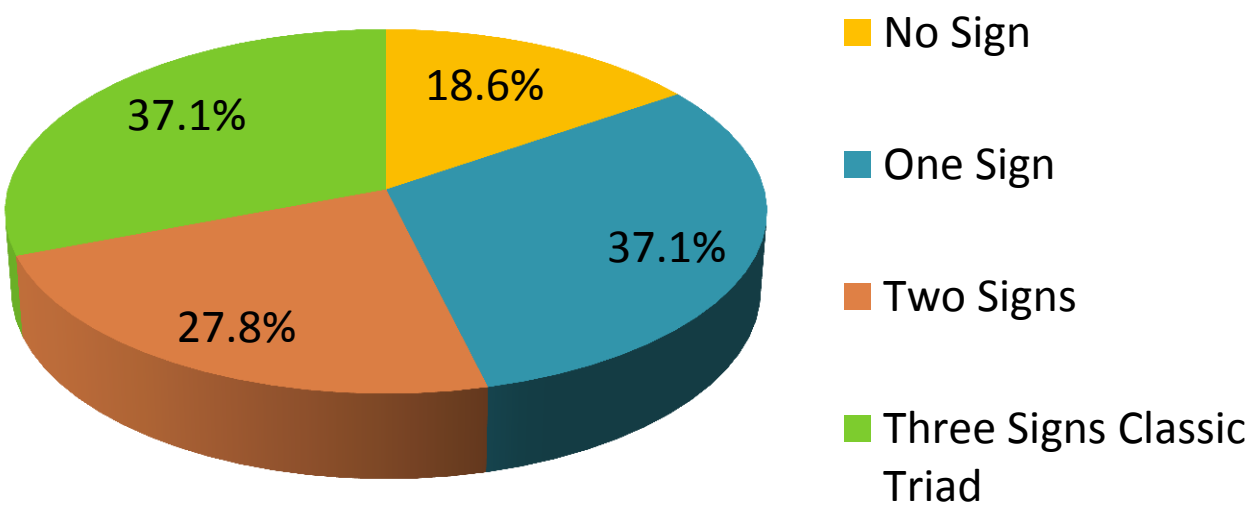
WKS: features

- Prerequisite is poor nutritional state
- Classic clinical triad
  - Encephalopathy:
    - Inattention, apathy, memory loss
    - Stupor or coma is rare
  - Ataxia: Trunkal > limb ataxia
  - Ophthalmoplegia:
    - Bilateral VI is commonest finding
    - Nystagmus and pupillary abnormalities

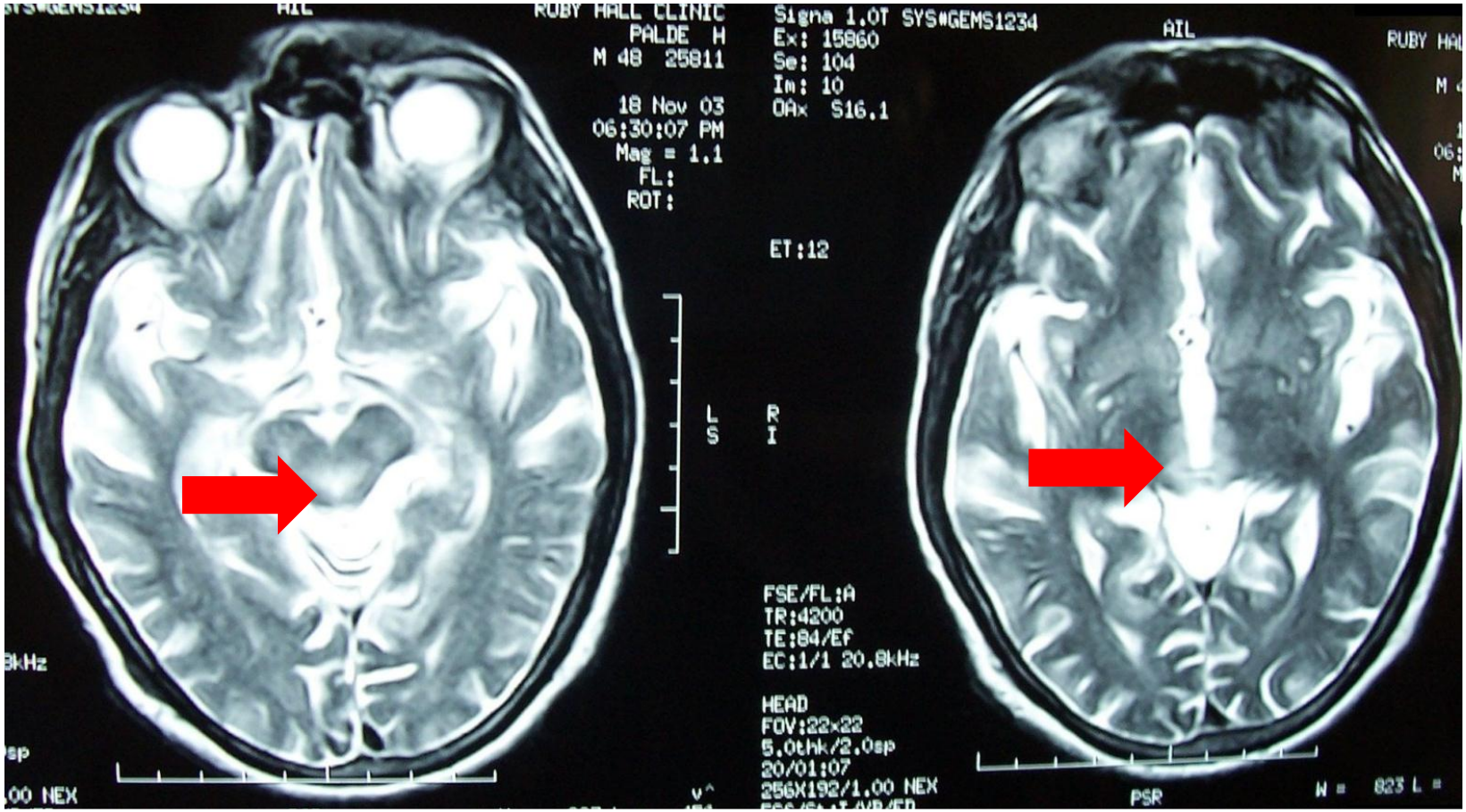
WKS: diagnosis

- Needs high degree of clinical suspicion
- Serum thaimine level can be measured
- MRI is characteristic
  - Hyperintense signal in
    - Periaqueductal region
    - Medial thalami
    - Mamillary bodies

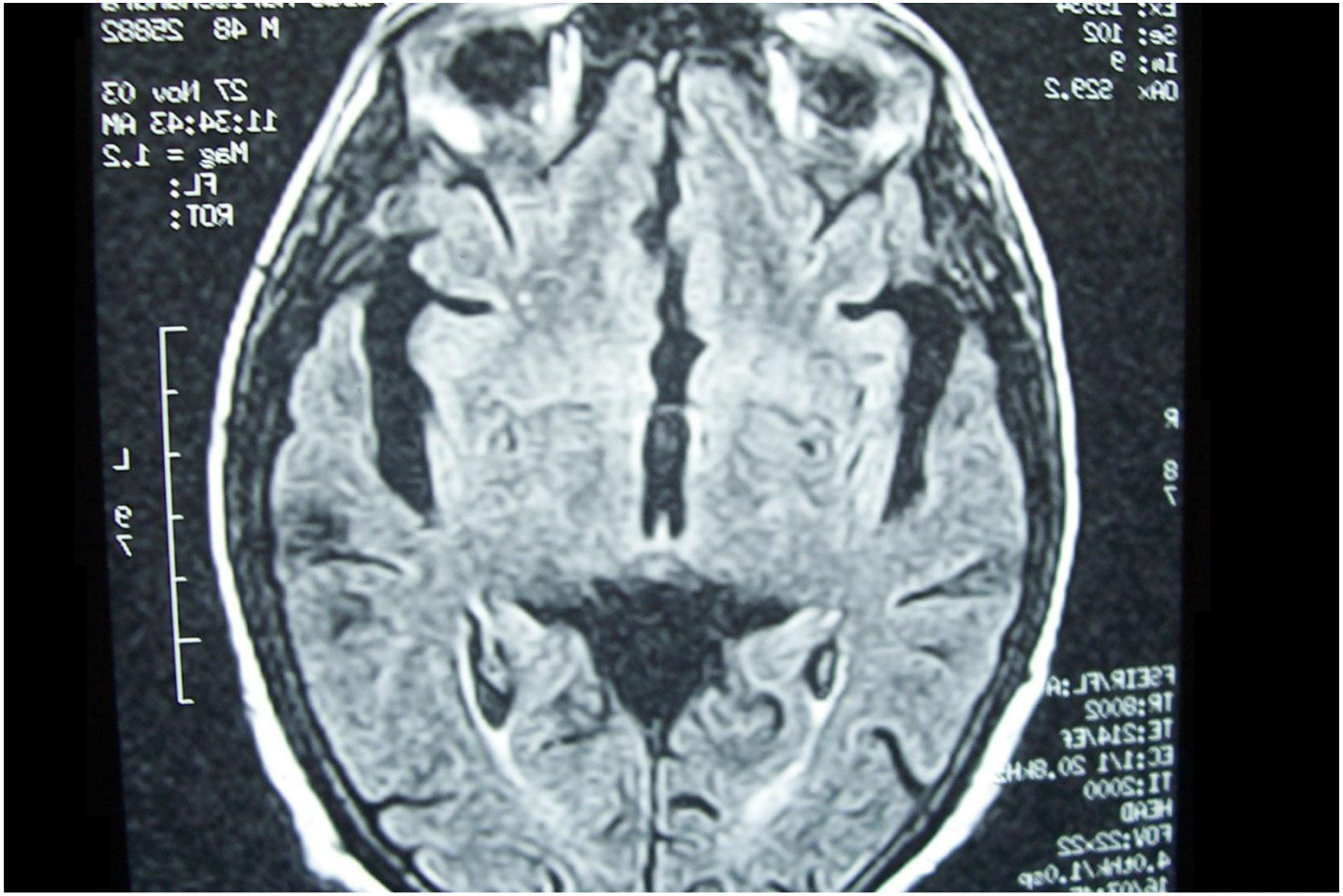
- The clinical diagnosis of WKS is missed in 80% of cases because many patients only exhibit one or two of the ‘classical’ clinical signs



WKS: MRI brain



WKS: MRI brain after treatment



WKS: treatment

- Thiamine 50 to 100 mg parenterally in acute stage
- Should be stated before giving any glucose
  - Glucose administration promotes dehydrogenation of pyruvate, a biochemical reaction which consumes thiamine
  - Hence encephalopathy can worsen
- Exact duration of treatment depends upon clinical response

WKS: prognosis

- Mortality 10 to 20%
  - Even in treated patients
- With treatment ocular signs resolve within hours and a fine nystagmus may persist in 60%
- Encephalopathy improves over days to weeks
- Ataxia resolves more slowly and 33% may have abnormal gait months after illness
- Some may develop Korsakoff's syndrome

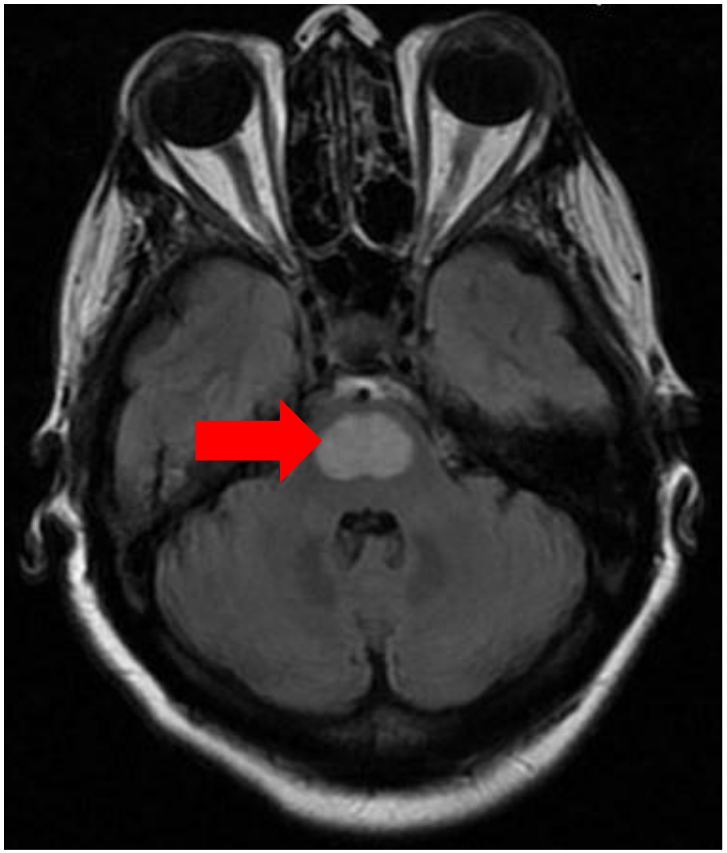
Central pontine myelinosis

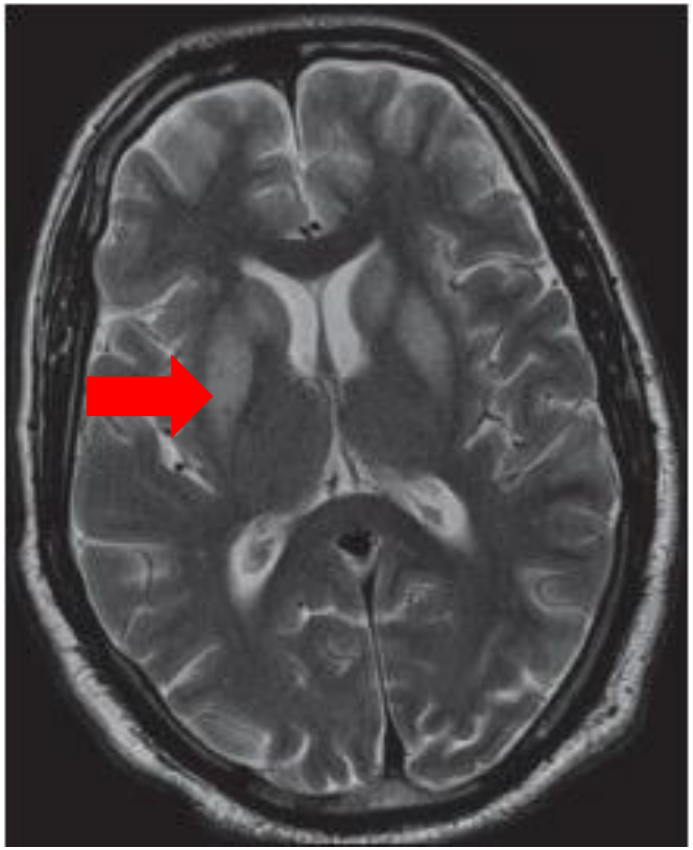
- Typically seen with rapid correction of hyponatraemia in alcoholics
  - Can occur in non-alcoholics as well
- Features
  - Alteration in seosorium
  - Quadriparesis
  - Eye movement abnormalities
- MRI shows myelinosis

Central pontine myelinosis

- Can involve other sites as well
  - Basal ganglion
  - Thalamus
  - Internal capsule
- Called extrapontine myelinosis
- Common terminology
  - Osmotic demyelination

MRI in osmotic demyelination





Hepatic encephalopathy

- Acute and chronic liver dysfunction is well known with alcoholism
- It manifests with hepatic encephalopathy
- Features
  - Change in personality, mood and behaviour
  - Slurred speech
  - Flapping tremor (asterixis)
  - Increased tone and hyperreflexia
  - Drowsiness progressing to coma

Hepatic encephalopathy

- Mechanism
  - Effect of elevated ammonia on neural membranes
  - Imbalance between excitatory and inhibitory neurotransmitters
  - Alteration in metabolism and levels of amino-acids (glutamine, glutamate, alanine, phenylalanine and tyrosine)
  - Inhibition of chloride extrusion
  - Neuronal depolarisation

Neurological drugs in treatment of alcoholism

- Topiramate
- Baclofen

Topiramate

- In doses up to 300 mg/day improved all drinking outcomes, decreased craving, improved quality of life

Baclofen

- Useful in management of both alcohol withdrawal syndrome and relapse prevention
- Suppresses symptoms of alcohol withdrawal syndrome; comparable with diazepam
- Effective in prevention of relapse due to its ability to reduce alcohol intake and craving
- No significant side effects; no addictive properties
- Dose: start with 20 mg/d; max 80 mg/d

‘Other’ substance abused

Factors affecting neurological manifestations

Directly due to drug

► A high dose	–sometimes because of an unusual source
► The speed of entry	–especially intravenous or when smoked
► Individual sensitivity	
► Chronic/repeated use	–for example, cocaine, leads to longer half life
► Interaction with other compounds in the drugs	
► Interaction with other drugs, including alcohol	
► Interaction with pre-existing pathologies	–hypertension, AVM, aneurysm, right to left cardiac shunt

Indirectly due to drug

► Secondary effects of coma or fits	–especially if aspiration occurs
► Infection risks	–easy portal of entry for pathogens –impairment of the immune system –exposures to pathogens such as HIV
► Accompanying lifestyle changes	–alcoholism –homelessness –prostitution –trauma*

*In my practice, the most common single neurological adverse effect of drug addiction is head trauma (for example, from baseball bats or gunshot wounds).

Types of substances abused

- Stimulants
- Sedatives
- Hallucinogens
- Organic solvents
- Drugs used to enhance athletic performance

1. Stimulants

- Amphetamines
- Cocaine
- Ephedrine
- Phenylpropanolamine
- Methylphenidate

Stimulants

- Motor manifestations
  - Tremors
  - Myoclonus
  - Seizures
- Neuropsychiatric manifestations
  - Restlessness
  - Irritability
  - Violence

Amphetamines

- Substances
  - Amphetamine
  - Meth-amphetamine (Methedrene)
  - 3,4-methylene-dioxy-amphetamine (MDA)
  - 3,4-methylene-dioxy-meth-amphetamine (MDMA, Ecstasy)
- Mechanism
  - Presynaptic release of monoamines
  - Excessive sympathetic stimulation

Neurology of amphetamines

- Stroke
  - Both ischemic and hemorrhagic stroeks can occur with amphetamines
  - Phenylpropanolamine is well know to cause hemorrhage
  - Mechanism
    - Acute increase in BP
    - CNS vasculitis

Neurology of amphetamines

- Dyskinesias and stereotypies
  - After acute or chronic usage
  - Types
    - Task repetition such as cleaning house, polishing the nails, or fidgeting with objects
    - Bruxism
    - Choreoathetoid movements
  - Cause: increased dopa and glutamate levels
  - Usually self limiting

Neurology of amphetamines

- Increased risk of Parkinson's disease
- Metabolic disturbances
  - Hyperthtrmia
  - Hyperglycemia
  - SIADH
  - Metabolic acidosis
- Wash-out syndrome
  - Somnolence, hyporeflexia, dysconjugate gaze

Cocaine

- Mechanism:
  - Blocks reuptake of monoamines
  - Local anaesthetic
- Stroke:
  - Both ischemic and hemorrhagic
  - Due to vasospasm, and prothrombotic state

Cocaine

- Seizures
  - With sudden and rapid drug intake
- Dystonia, chorea
- Dementia
  - Chronic cocaine use has been associated with cognitive impairment
  - Many of these patients have multiple infarcts or ischemic lesions
- Effects on fetal development

2. Sedatives

- Opioids
- Barbiturates
- Other sedatives

Opioids

- Can be agonists, antagonists or mixed agonist-antagonists
- Opioid agonists
  - Drowsy euphoria
  - Analgesia
  - Cough suppression
  - Miosis, nausea, vomiting, sweating, pruritus, hypothermia, postural hypotension, constipation, and decreased libido

Opioids

AGONIST
Tincture of opium (laudanum)
Camphorated tincture of opium (paregoric)
Morphine (morphine sulfate injection; MS Contin, Oramorph)
Heroin (legally available only for investigational use)
Methadone (Dolophine)
Fentanyl (Sublimaze, in Innovar, Duragesic patch)
Sufentanil (Sufenta)
Alfentanil (Alfenta)
Oxymorphone (Numorphan)
Hydromorphone (Dilaudid)
Codeine
Oxycodone (Oxy-Contin; in mixtures, e.g., Percodan, Percocet, Tylox)
Hydrocodone (in mixtures, e.g., Hycodan, Lortab, Lorcet, Tussionex, Vicodin)
Levorphanol (Levo-Dromoran)
Meperidine (pethidine; Demerol, Pethadol)
Propoxyphene (Darvon; in Darvocet, Wygesic)

ANTAGONIST
Naloxone (Narcan)
Naltrexone (Trexan)
Nalmefene (Revex)
MIXED AGONIST–ANTAGONIST
Pentazocine (Talwin, Talwin Nx, in Talacen)
Butorphanol (Stadol)
Buprenorphine (Buprenex)

Opioids

- Overdose causes coma, respiratory depression, and pinpoint pupils
- Withdrawal produces irritability, lacrimation, rhinorrhea, sweating, yawning, mydriasis, myalgia, muscle spasms, piloerection, nausea, vomiting, abdominal cramps, fever, hot flashes, tachycardia, hypertension, orgasm
  - Seizures and delirium are not features of opioid withdrawal

Neurology of opioids

- Stroke
  - Heroin users are prone to stroke due to multiple reasons
    - Endocarditis
    - AIDS
    - Angitis
    - Related to liver or kidney disease
    - Embolization of foreign material

Neurology of opioids

- Myelopathy: seen with heroin
  - Presents with paraparesis, sensory loss, and urinary retention
- Neuropathy
  - Due to toxic or immunlogic mechanism
  - Sec to AIDS, antiretroviral therapy, ethanol abuse, malnutrition, injection into nerves, and pressure
- Muscle disease
  - Rhabdomyolysis secondary to injections

Neurology of opioids

- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
  - Sold as synthetic heroin
  - Parkinson's disease

3. Hallucinogens

- Marijuana
- Phencyclidin
- LSD
- Ketamine
- Gamma hydroxybutyrate

Marijuana

- 9 tetrahydrocanabinol
- Mechanism
  - Presynaptic inhibition of release of neurotransmitters
- Has been used for management of pain

Neurology of marijuana

- Marijuana antimotivational syndrome
  - Apathy, decreased attentiveness, and memory impairment
- Conflicting evidence of cognitive impairment with chronic marijuana use

Other hallucinogens

- Phencyclidin
  - Frontal lobe syndrome
- d-lysergic acid diethylamide (LSD)
  - Hallucinations
- Ketamine
  - Dissociative anesthesia

4. Organic solvents

- Glue sniffers
- Used by teens and children for abuse
- Used in various industries

Abused Inhalants and Their Contents

Products	Contents
Aerosols (refrigerants, cleaners, hair sprays, deodorants, antiseptics)	Aliphatic and halogenated hydrocarbons
Dry-cleaning fluids, furniture polish	Halogenated hydrocarbons, naphtha
Glues, cements	Toluene, acetone, benzene, xylene, n-hexane, trichloroethylene, butyl alcohol, methylethylketone, chloroform, triorthocesyl phosphate, ethanol
Paints, lacquers, paint and lacquer thinners	Toluene, methylene chloride, aliphatic acetates, ethanol
Lighter fluid	Aliphatic and aromatic hydrocarbons
Fire-extinguishing agents	Halogenated hydrocarbons
Nail-polish remover	Acetone, aliphatic acetates, benzene
Typewriter correction fluid	Trichloroethane, trichloroethylene
Marker pens	Toluene, xylene
Bottled fuel gas, natural gas	Butane, propane, methane, ethane
Mothballs	Naphthalene, paradichlorobenzene
Petroleum	Aromatic and aliphatic hydrocarbons, tetraethyl lead
Anesthetics	Nitrous oxide, diethyl ether, halothane, enflurane, trichloroethylene
Room odorizers	Amyl, butyl, and isobutyl nitrite

Neurology of organic solvents

- Toluene
  - Cerebellar ataxia
  - Dementia
- Hexane
  - Peripheral neuropathy
- Nitrous oxide
  - Myeloneuropathy like SACD
- Nitrites
  - Headache

5. Drugs used to enhance athletic performance

- Anabolic effects (steroids, insulin, growth hormone)
- Stimulants to heighten alertness, reduce fatigue, and prolong endurance (amphetamines, cocaine)
- Erythropoeitin to increase haemoglobin and oxygen delivery in endurance sports
- Beta2 agonists for supposed ‘‘fat-burning’’ effects

Neurology of performance enhancers

- Uncommon

Drug	Relevant adverse effects
Anabolic steroids	Cardiovascular, including hypertension and presumably strokes
Growth hormone*	Carpal tunnel
Insulin	Hypoglycaemia
Erythropoeitin	Headaches, encephalopathy, strokes, seizures
Clenbuterol	Tremor, headaches
Cocaine and amphetamines	As earlier

Summary

ETHANOL: Pathologic intoxication

Withdrawal syndrome and delirium tremens
Seizures
Cerebellar degeneration
Wernicke-Korsakoff syndrome
Dementia
Polyneuropathy
Myopathy
Stroke
Fetal alcohol syndrome

AMPHETAMINE, PCP

Agitation
Paranoid psychosis
Seizures
Hypertension
Focal neurologic deficit
Movement disorder

BENZODIAZEPINES

Drowsiness
Ataxia
Hypotension
Syncope
Headache
Dysarthria
Confusion
Amnesia
Withdrawal seizures

COCAINE

Delirium
Headache
Syncope
Focal neurologic deficit
Schizophreniform psychosis
Polyneuropathy, myelopathy

OPIATES AND BARBITURATES

Drowsiness
Disorientation
Dysarthria
Ataxia
Nystagmus
Respiratory depression
Coma

Thank You

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