

Alcohol related brain disorders

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(GP Forum)



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Objectives

- **Definition**
- **Epidemiology**
- **Classification**
- **Types and symptomatology**
- **Pathology**
- **Management**
- **Complications**



Dementia - definition

- Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment.
- The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.



Epidemiology of dementia

- Prevalence and incidence increases with age.
- 700,000 people suffer from dementia in UK.
- This amounts to 5% of total population above 65 and 20% of population above 80.
- Dementia costs the UK economy £17 billion / year.
- In 30 years number of people with dementia will double to 1.4 million, trebling the costs to £50 billion / year.



Epidemiology of dementia

- People live for 7-12 years after the diagnosis.
- The rate for “treated incidence” is reported between 1.9-2.6/1000 for men and 2.1-4.1/1000 for women. True incidence of treatable cases is 10-16/1000 for both sexes.
- There is a relative excess of Alzheimer’s disease (AD) among women and of vascular dementia (VaD) among men.



Epidemiology of ARBD

- A study found alcohol-related brain changes in around 1.5% of the general population and 30% in heavy drinkers (1998).
- A study of WE (Wernicke's Encephalopathy) found the condition in up to 2.8% of the general population and 12.5% of alcoholics (1997).
- A report states that 160,181 prescription items for drugs for the treatment of alcohol dependency were prescribed during 2010 (NHS Alcohol Statistics Report, 2011).
- This was an increase of 6% for 2009 figure (150,445) and an increase of 56% for 2003 figure (102,741).



Epidemiology of ARBD

- Lifetime prevalence of WKS (Wernicke's Korsakoff's psychosis) is between 0.1% and 1% across the population, with a UK rate of 0.5%.
- Lifetime prevalence of WE is 1.5%, but with rates varying from 0.4% (France) to 2.8% (Australia).
- Prevalence of alcohol-related dementia was 8.3/100,000 in the 30-64 year old population, (95% CI 4.7-13.4); 12.5% of all young onset dementia cases were alcohol related dementia (London).
- Of young onset dementia cases, 12.3% were alcohol related (Lothian, Scotland).



Epidemiology of ARBD

- Prevalence of ARD amongst over 50s newly admitted to hospital was 1.4% across all patients with dementia but 22% for those under 65 (Australia).
- Significantly more care home residents with early onset dementia had the condition as a result of alcohol than residents with dementia onset after 65 (USA).
- Annual incidence for KS amongst admissions to a psychiatric hospital and a general hospital rose from 1.3/100,000 in 1990 to 8.1/100,000 in 1995 (Glasgow)



Prevalence of ARD

- A review by Ritchie and Villebrun¹ established that studies have indicated a high prevalence of alcohol abuse in patients with dementia (9% to 22%) and high rates of dementia in alcohol abusers (10% to 24%), although most studies did not specify the type of dementia. *1. Epidemiology of alcohol-related dementia.* Ritchie K, Villebrun D *Handb Clin Neurol.* 2008; 89():845-50.
- ARD cases generally have a younger age of onset, and consequently studies that exclude those under 60 years of age may miss a significant proportion of cases.
- ARD accounted for 10-24% of all dementias amongst care home residents and 3-5% of dementias diagnosed in neurology and memory clinics (review of evidence from several countries).
- Rates of ARD of around 10% were found in an English epidemiological study² of younger-onset dementia in specific London districts (onset of less than 65 years). *2. The prevalence and causes of dementia in people under the age of 65 years.* Harvey RJ, Skelton-Robinson M, Rossor MN *J Neurol Neurosurg Psychiatry.* 2003 Sep; 74(9):1206-9.



Different types / stages

- Alcohol induced amnesic syndrome
- Wernicke's Encephalopathy
- Wernicke's Korsakoff's Psychosis
- Alcohol related dementia
- Marchiafava-Bignami disease
- Central Pontine Myelinosis



Terminology

- The DSM-IV describes 'alcohol-induced persistent dementia', as progressive intellectual and cognitive decline without a profound amnestic disorder.
- The term 'alcoholic dementia' has been generally superseded by the concept of alcohol-related dementia, encompassing a broader definition of alcohol-related cognitive deficits.
- This distinction may have implications for the prognosis and treatment of patients, as evidence suggests that alcohol-related dementia is less progressive than Alzheimer's disease.
- Treatment for alcohol misuse and selection of residential placements are quite pertinent in these patients and needs may differ from those with other forms of dementia patients.



Diagnostic guidelines for Alcohol related amnesic syndrome

- Amnesic syndrome induced by alcohol or other psychoactive substances should meet the general criteria for organic amnesic syndrome.
 - The primary requirements for this diagnosis are:
 - (a) memory impairment as shown in impairment of recent memory (learning of new material); disturbances of time sense (rearrangements of chronological sequence, telescoping of repeated events into one, etc.); presence of confabulation but not invariable for diagnosis.
 - (b) absence of defect in immediate recall, of impairment of consciousness, and of generalized cognitive impairment;
 - (c) history or objective evidence of chronic (and particularly high-dose) use of alcohol or drugs.
- Other cognitive functions are usually relatively well preserved and amnesic defects are out of proportion to other disturbances.



Diagnostic guidelines for Alcohol related amnesic syndrome

- **Personality changes, often with apparent apathy and loss of initiative, and a tendency towards self-neglect, but should not be regarded as necessary conditions for diagnosis.**
- **Includes: Korsakov's psychosis or syndrome, alcohol or other psychoactive substance-induced.**



DSM V Diagnostic criteria

Alcohol-Induced Neurocognitive Disorder shows cognitive decline from a previous level of performance in one or more cognitive domains of higher cortical functioning:

- a. Learning and memory**
- b. Complex attention**
- c. Executive function (e.g., impaired planning, organizing, sequencing, abstracting)**
- d. Language (e.g., aphasia)**
- e. Perceptual-motor (e.g., agnosia [failure to recognize or identify objects despite intact sensory function], or apraxia [impaired ability to carry out motor activities despite intact motor function])**
- f. Social cognition**



ARBD – Neurological impairment

| Neuropathology | Impairment |
|---------------------------|--|
| Peripheral neuropathy | Poor mobility & dexterity |
| Hepatic encephalopathy | Chronic liver disease toxins leading to progressive memory loss, disorientation, tremors & dementia |
| Frontal lobe impairment | Behavioural changes; eg. disinhibition, aggression, irritability or impulsivity, “Impulse Control Disorder ” |
| Wernicke's Encephalopathy | Acute neurological disorder due to thiamine (Vitamin B1) deficiency |
| Korsakoff's dementia | Severely impaired mentation |
| Cerebellar atrophy | Poor balance and gait |



Wernicke's encephalopathy

- There is strong hypothesis that thiamine (vitamin B1) deficiency is primarily responsible for the development of (ARD).
- Individuals with alcohol use disorders are at particularly high risk of thiamine deficiency, not only from poor dietary nutrition but because alcohol directly compromises thiamine metabolism.
- Thiamine deficiency can lead to Wernicke's encephalopathy, an acute neurological disorder characterized by the clinical triad:
 1. Oculomotor abnormalities
 2. Cerebellar dysfunction
 3. Altered mental state.
- There is neuronal loss and hemorrhagic lesions in the paraventricular and periaqueductal grey matter.



Korsakoff's syndrome

- Long-term outcomes of WE can include development of a syndrome of profound memory impairment – KS - that appears to be related to additional disruption to diencephalic and hippocampal circuitry.
- As KS shares similar pathological substrates and often follows an episode of WE, it is commonly referred to as the WKS.
- The heterogeneity in presentation of the WKS, in combination with a lack of distinct pathological evidence for ARD, has led to the suggestion that cases of ARD are variants of the WKS.
- Other evidence suggests that ARD and WKS are distinct disorders with overlapping clinical symptoms and associations such as peripheral neuropathology and ataxia.



Clinical presentation of KS

- Patients typically demonstrate profound anterograde amnesia and impaired recall of past events.
- Implicit memory and procedural memory are comparatively spared.
- Other cognitive functions apart from memory may be disturbed, and impaired executive functions, visuoperceptual difficulties, and disturbed working memory have been observed.
- Executive deficits have been identified in 80% of patients with KS.
- Difficulties are most frequently detected on tasks assessing higher-order organization, planning, and cognitive flexibility (for example, verbal fluency and divided attention).



Treatment of WKS

- Royal College of Physicians have suggested 500 mg of Thiamine intravenously 3 times a day for 2-3 days.
- If no response is noted, discontinue supplementation and assess for supportive care (unless the patient is comatose). If there is a partial response, continue at 250 mg parenterally for 5 days or as long as improvement continues in patients with neuropsychiatric symptoms.



ARD - Pathology

- Harper³ has reported a statistically significant loss of brain tissue in chronic alcoholics compared with controls.
- This loss appears to be primarily from the white matter with reduction in the number of cortical neurons in the superior frontal cortex, hypothalamus and cerebellum; but not in basal ganglia, nucleus basalis, or serotonergic raphe nuclei.
- This seems to occur independently of WE but nutritional deficits may make the situation worse.
- Chronic alcoholism inhibits N-methyl-D-aspartate (NMDA) causing upregulation of the NMDA subtype of glutamate receptors in the frontal cortex, which reflects alcohol-induced chronic neurotoxicity with increased intracellular calcium (mediating oxidative stress) along with loss of cholinergic muscarinic receptors. This may be related to the clinical symptoms of alcohol withdrawal and alter seizure activity in the brain.

3. Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J Neuropathol Exp Neurol 1998; 57: 101 -10



ARD - Pathology

- A review on the effect of alcohol on the frontal lobe noted that neuroradiological findings support the occurrence of morphological abnormalities in brains of chronic heavy drinkers, suggesting cerebral atrophy⁴.
- Structural imaging using computed tomography scans of male alcoholics showed larger ventricles and wider cerebral sulci and fissures compared with controls⁵.
- Functional imaging studies have reported decreased frontal lobe glucose utilisation and reduced cerebral blood flow⁶.
- Women are probably more vulnerable to the effects of alcohol, exhibiting earlier changes but also faster recovery on abstinence⁶.

4. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism. *Alcohol Alcohol* 2001; **36**: 357-68.

5. Pfefferbaum A, Rosenbloom M, Crusan K, Jernigan TL. Brain CT changes in alcoholics: effects of age and alcohol consumption. *Alcohol Clin Exp Res* 1998; **12**: 81-7.

6. Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, Diehl A. Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? *Alcohol Clin Exp Res* 2005; **29**: 896-901.



ARD - Pathology

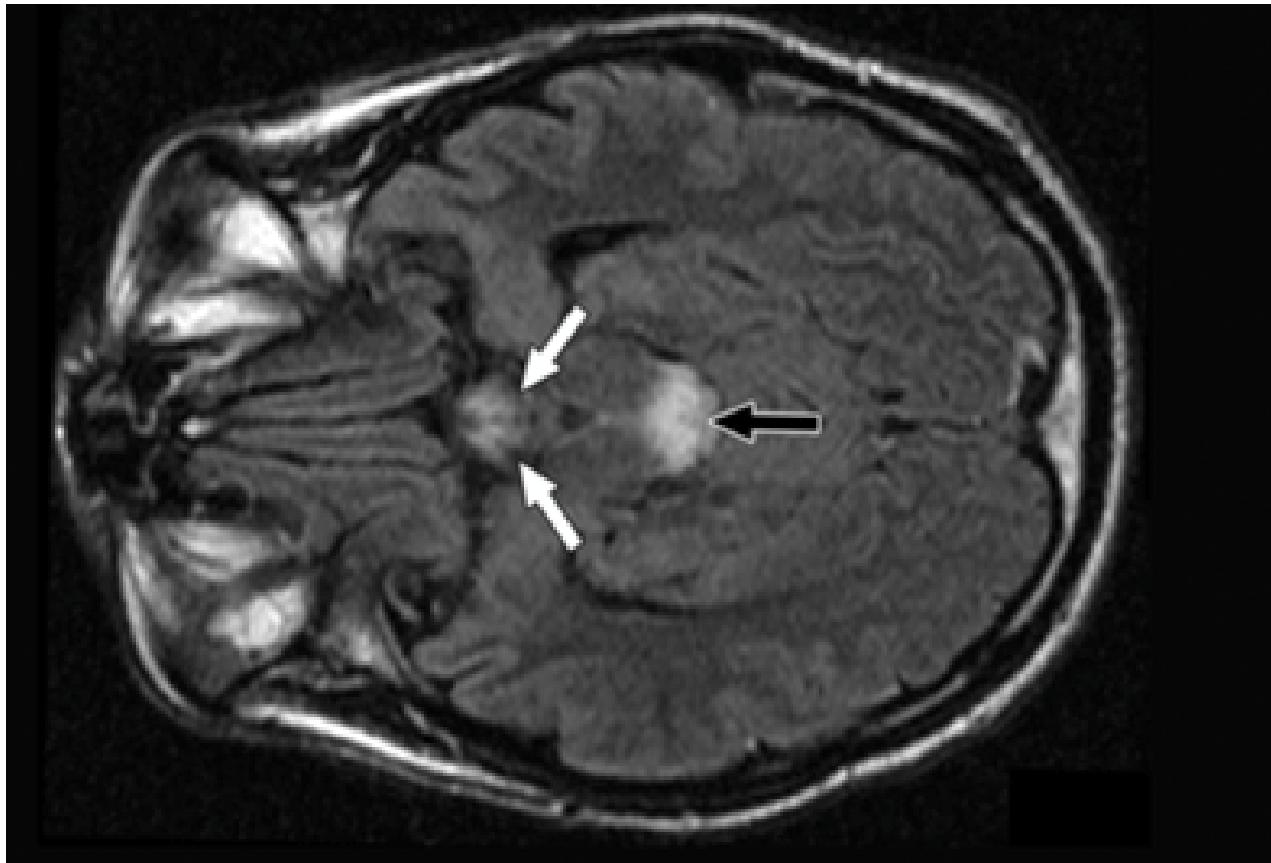
- Various mechanisms have been attributed to the effects of alcohol on the brain including a direct neurotoxic effect of alcohol, oxidative stress, excitotoxicity, mitochondrial damage and apoptosis.
- Repeated withdrawal may be associated with greater cognitive impairment due to neuronal damage and may have a bearing on the dementing process.
- Those having two or more detoxifications showed a greater degree of cognitive impairment compared with those with one or none⁷.
- Repeated withdrawals may be associated with 'kindling-effect' of worsening of withdrawal symptoms and associated brain damage.
- A study found structural brain changes in treatment-naïve alcoholics to be less severe than those of clinical samples of alcoholics⁸.

7. Duka T, Townshend JM, Collier K, Stephens DN. Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. *Alcohol Clin Exp Res* 2003; **27**: 1563 - 72.

8. Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcohol Clin Exp Res* 2002; **26**: 558-64.



Neuroimaging - MRI



White arrows showing high signal intensity in mammillary bodies and black arrow periaqueductal area



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ARD – Indirect impact of alcohol on brain

- Drinking leads to raised triglycerides, hypertension and other factors, which could contribute to adverse cerebrovascular changes.
- Chronic alcoholism has been linked with hyperhomocysteinaemia – considered toxic to the endothelium and associated with increased risk of arterial thrombosis, cardiac disorders and strokes⁹.
- Consuming more than six drinks per week is also associated with increased risk of ischemic stroke and lacunar infarcts, which further increased in those who are apoE4 positive¹⁰.
- Hepatic encephalopathy in chronic alcoholics, raised toxins like ammonia and manganese can all exert harmful effects which interfere with normal neurotransmitter activity, impair motor functions, and cause structural alterations in the astrocytes, which have neuroprotective functions.

9. Bleich S, Degner D, Javaheripour K, Kurth C, Kornhuber J. Homocysteine and alcoholism. *J Neural Transm* 2000; **60**: 187 -96.

10. Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth WT, Mittleman MA, Burke GL, Cushman M, Beauchamp NJ, Siscovick DS. Alcohol use and risk of ischemic stroke among older adults: the Cardiovascular Health Study. *Stroke* 2005; **36**: 1830-4.



How much drink is actually problematic???

- A standard drink in the United Kingdom contains a relatively low 8 grams of alcohol, compared with 10 grams in Australia, 14 grams in the US, and 19.75 grams in Japan.
- Reduced frontal lobe volume has been associated with an amount of 418 grams a week but has not correlated with lower levels of consumption.
- One review suggested that consumption of five to six drinks per day (which, by US standards, equates to 70 to 84 grams) over extended periods results in 'cognitive inefficiencies', while consumption of 10 or more standard drinks a day manifests as moderate cognitive deficits equivalent to that found in individuals with diagnosed alcoholism.



How much drink is actually problematic???

- Oslin and colleagues¹¹ suggested that a five-year history of consuming 35 standard drinks a week for men and 28 for women constitutes a sufficient level of neurotoxic burden to risk the development of ARD.
- Heavier drinking may contribute to adverse cerebrovascular changes (hypertension and raised triglycerides) and increased risk of arterial thrombosis, cardiac disorders, and strokes¹².

11. Alcohol related dementia: proposed clinical criteria. Oslin D, Atkinson RM, Smith DM, Hendrie H. *Int J Geriatr Psychiatry*. 1998 Apr; 13(4):203-12.

12. Alcohol-related dementia: a 21st-century silent epidemic? Gupta S, Warner J. *Br J Psychiatry*. 2008 Nov; 193(5):351-3.



Alcohol units

One unit of alcohol is about equal to:

- Half a pint of ordinary strength beer, lager, or cider (3-4% alcohol by volume); or
- A small pub measure (25 ml) of spirits (40% alcohol by volume); or
- A standard pub measure (50 ml) of fortified wine such as sherry or port (20% alcohol by volume).

There are one and a half units of alcohol in:

- A small glass (125 ml) of ordinary strength wine (12% alcohol by volume); or
- A standard pub measure (35 ml) of spirits (40% alcohol by volume).

Generally 1 unit = 8gm = 10ml of pure alcohol.

Unit = Volume x ABV

1000



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What does 1 unit of alcohol look like?



Standard
4.5% cider



Standard
13% wine



Standard
40% whiskey



Standard
4% beer



Standard 4%
alcopop (275ml)



You shouldn't
regularly exceed



drinkaware.co.uk



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ARD and other types of dementia

| ARD | Other dementias |
|--|--|
| Unlikely to demonstrate language impairment | More likely language impairment |
| ARD groups generally performed better on semantic tasks such as confrontational naming, category fluency, and general knowledge | AD generally respond poorly on semantic tasks |
| ARD groups had poorer performance on visuospatial measures, including clock drawing and copying tasks | Other dementias perform better on these tasks |
| | |



Investigations

- Specialist neuropsychometric testing can reveal deficits in working memory, cognitive flexibility, problem solving and perseveration.
- Blood tests can be ordered if one suspects underlying Alzheimer's disease (FBC including MCV, MCHC, LFTs, liver enzymes, B12, folate, RBC and transketolase) and MRI should be used to support diagnosis. Structures that are affected include mammillary bodies, corpus callosum, frontal lobe, thalamus and cerebellum.
- Specific sequences are required and an expert opinion should be sought from a neuroradiologist.
- Having established the presence of brain damage, diagnosis of ARBD can be assisted by a process of eliminating other potential causes of the damage.



Investigations

- WKS involves damage to specific areas in the brain, for example, petechial haemorrhage in the periaqueductal grey matter and volume changes in the mammillary bodies.
- Neuropathological studies have revealed that damage to the anterior nucleus of the thalamus accounts for Korsakoff's psychosis and patients with non-amnesic WE also have damage to this area, but it is less severe.
- Amnesia is probably caused by interruption to the diencephalic-hippocampal circuit including thalamic nuclei and mammillary bodies, rather than a single lesion in the anterior thalamic nucleus.



Clinical management

- A thorough nutritional and drinking history should be taken, with confirmation from an informant if possible.
- All individuals with any evidence of chronic alcohol misuse and suspected of having WE should be treated immediately with parenteral thiamine.
- Treatment with oral thiamine is ineffective because it does not achieve an adequate plasma concentration.
- While there is no consensus as to the optimum dose, frequency, route, and duration of thiamine treatment, in the cases of suspected WE, thiamine be given in doses of 200 mg three times daily, preferably intravenously. This treatment should be continued until no further improvement in signs and symptoms is evident.



Clinical management

- Assessment of cognitive status should be conducted on an ongoing basis as this will allow any improvement, stabilization, or deterioration to be detected.
- Acute intoxication and withdrawal may exacerbate cognitive deficits, so assessment following this period (which usually lasts no longer than 2 weeks) may allow a more accurate baseline to be established.
- Key characteristics associated with alcohol-related cognitive disorders typically involve stabilization or improvement in cognition with abstinence; a cognitive profile involving executive, visuospatial, and memory difficulties with spared language function; and neurological symptoms such as ataxia.
- Neuroimaging may suggest atrophy in the mammillary bodies, thalamus and cerebellum, and ventricular enlargement, although this may vary from case to case.
- Patients with ARD and WKS have shown cognitive improvement following treatment with memantine, although these findings require replication^{13,14}.

13. The effect of 12-week open-label memantine treatment on cognitive function improvement in patients with alcohol-related dementia. Cheon Y, Park J, Joe KH, Kim DJ *Int J Neuropsychopharmacol*. 2008 Nov; 11(7):971-83.

14. A placebo-controlled study of memantine (Ebixa) in dementia of Wernicke-Korsakoff syndrome. Rustembegović A, Kundurović Z, Sapcanin A, Sofic E *Med Arh*. 2003; 57(3):149-50.



Marchiafava-Bignami disease

- **Marchiafava-Bignami disease (MBD) is a rare condition characterized by demyelination of the corpus callosum.**
- **It is seen most often in patients with chronic alcoholism.**
- **In 1903, Italian pathologists Marchiafava and Bignami described 3 alcoholic men who died after having seizures and coma.**
- **In each patient, the middle two thirds of the corpus callosum was found to be severely necrotic.**
- **Most of these men were “alcoholic”.**



Central pontine myelinolysis

- Adams et al described central pontine myelinolysis (CPM) as a unique clinical entity.
- They published their findings in 1958, observing that patients who suffered from alcoholism or malnutrition developed spastic quadriplegia, pseudobulbar palsy, and varying degrees of encephalopathy or coma from acute, noninflammatory demyelination that centered within the basis pontis.
- Physicians currently recognize that central pontine myelinolysis occurs inconsistently as a complication of severe and prolonged hyponatraemia particularly when corrected too rapidly.
- Standard of care requires judicious treatment of electrolyte disturbances to reduce the incidence of osmotic myelinolysis.



Other substances

- Mental and behavioural disorders due to use of opioids.
- Mental and behavioural disorders due to use of cannabinoids.
- Mental and behavioural disorders due to use of sedatives and hypnotics.
- Mental and behavioural disorders due to use of cocaine.
- Mental and behavioural disorders due to use of stimulants like caffeine.
- Mental and behavioural disorders due to use of hallucinogens.
- Mental and behavioural disorders due to use of tobacco.
- Mental and behavioural disorders due to use of volatile substances.
- Mental and behavioural disorders due to use of multiple drugs and other psychoactive substances.



Just a few things to keep in mind

- ARD is one of the common forms of dementia among the young onset dementia cohort.
- The condition seems to be on the rise.
- It is one of the ‘treatable’ causes of dementia if picked up early. But depends on motivation, contemplation and willingness of the individual and support in community and family.
- The pathological areas in brain can be an overlap with other forms of dementia although some distinction can be drawn.
- Opportunities of psychoeducation must not be missed during the recovery phase of WE / withdrawal.



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