

Movement Disorders in Chronic Kidney Disease

Bahman Jabbari M.D.
Emeritus Professor of Neurology
Yale University School of Medicine

Definition

- Movement disorders are involuntary abnormal movements usually caused by dysfunction of basal ganglia or other subcortical structures.
- They can be classified into hyperkinetic and hypokinetic categories.
- Hypokinetic movement disorders include bradykinesia (slowness of movement) and hypokinesia (paucity of movement).

Lecture Outline

- Brief discussion of how chronic kidney disease (CKD) can cause diffuse cortical and subcortical damage of structures known to produce abnormal movements.
- Description of common hyperkinetic movement disorders in CKD: Restless legs syndrome (RLS), chorea, myoclonus, asterixis
- Discussion of parkinsonism, hypokinesia and bradykinesia in CKD

Brain Cellular Damage in CKD

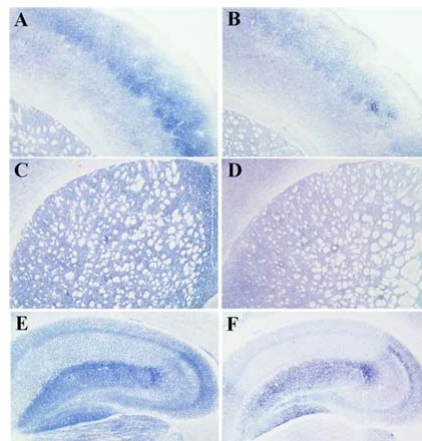
- In CKD, interaction of reactive oxygen species with nitric oxide leads to accumulation of toxic nitrotyrosine in cortical and subcortical structures damaging DNA and proteins (Deng, Vaziri, Jabbari et al 2001).
- CKD results in activation of inflammatory and oxidative pathways, inhibition of antioxidant and cytoprotective system as well as erosion of cerebral capillary junctional complex in cerebral tissue- events that contribute to CNS dysfunction and impaired blood brain barrier (Jing, Jabbari, Vaziri et al 2018).

Brain Cell Damage Associated with CKD

- Elevated urea in CKD alters the actin cytoskeleton and tight junction proteins in cultured endothelial cells leading to disruption of blood-brain barrier resulting in increased incidence of brain microhemorrhages. (Lau et al, 2020).
- Increased intracellular calcium, due to hyperparathyroidism, can cause diffuse cortical and subcortical cell dysfunction in CKD (Smogorewski et al, 1995)

- Tissue examination in adenine rich diet mouse model of CKD shows diffuse inflammatory changes, evidence of significant oxidative stress, loss of brain cholinesterase activity and impaired mitochondrial function in cerebral cortex and basal ganglia.

Mazumder et al, 2019



Mitochondrial complex II
A& B cortex, C&D basal ganglia, E & F hippocampus

Restless Leg Syndrome (RLS)

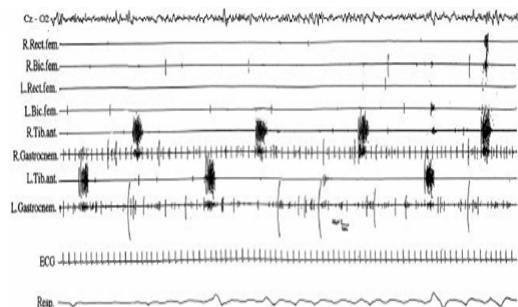
- Restless legs syndrome (RLS) is a movement disorder characterized by an urge to move the legs or arms, commonly in response to uncomfortable dysesthesia.
- Dysesthesias are most noticeable during afternoon and evenings. Moving the legs, often relieves the unpleasant limb sensations.

Winkelman et al. Neurology. 2016; Vol 87

BJ4

Restless Legs Syndrome (RLS)

- Over 90% of patients with RLS demonstrate periodic leg movements (PLM) during sleep.
- PLM consists of intermittent, involuntary dorsiflexion of the foot, flexion of the knee and thigh with a periodicity of every 20-40 seconds.



Provini et al. Neurology 2001, 57(2)

DO NOT COPY

Restless Legs Syndrome

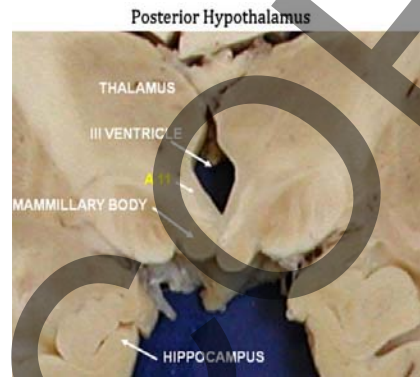
- The disturbing evening leg sensations and urges to move, periodic leg movements during sleep that often lead to delay in sleep onset, interrupted sleep, awakening and daytime sleepiness, collectively impair patients' quality of life.
- The incidence of both coronary artery disease and cerebrovascular disease is twice higher in patients with RLS compared to patients with sleep complaints without RLS (Winkelman et al, Neurology 2008).

Essential vs Secondary RLS

- Essential RLS is seen in 5-10% of general population (Allen et al. Sleep Med , 2010). Women are more frequently affected.
- Clinical and paraclinical evidence indicates that essential RLS results from decreased brain content of iron which, in many cases, is genetically determined. Ultrasound and MRI show low iron content of putamen, thalamus, red nucleus and substantia nigra (Rizzo et al. 2013; Mon et al. 2014)
- Iron is a co-factor for tyrosine hydroxylase, an enzyme that converts tyrosine to dopamine. Basal ganglia are rich in dopamine, a major neurotransmitter. Lack of dopamine causes sensory/motor disturbance such as seen in RLS and Parkinson's disease (PD).

The Site of Dopamine Loss in Restless Legs Syndrome

- The site of dopamine loss in RLS is believed to be Area 11, a part of hypothalamus, a subcortical region that directly projects to the spinal cord. This region of dopamine loss is different from that found in Parkinson's disease which is substantia nigra of midbrain and nigrostriatal system.



- Early et al. Sleep Med 2009;10: 1115-1117

Secondary RLS

- RLS can occur in a variety of medical conditions such as iron deficiency states, peripheral neuropathy, vitamin deficiency syndromes and in chronic kidney disease (CKD).
- The incidence of RLS in CKD increases with deterioration of kidney function. It affects 21-30% of dialysis patients (Molnar et al 2005; Merlino et al 2008; Araujo et al 2010). In one study, 51% of the recipients of kidney transplantation had RLS (Naini et al 2015).

RLS in CKD

- The cause of RLS in CKD is multifactorial: Metabolic dysfunction of subcortical structures in CKD, iron deficiency, & uremic neuropathy.
- Restless leg syndrome in CKD is associated with increased risk for all-cause mortality 1.69 [1.04-275] (Ricardo et al, Kidney Int Rep 2017).

Treatment of Restless Legs Syndrome

Name of drug	Dose in RLS without CKD	Recommended Dose in CKS	References based on blinded RCTs
Pramipexole	0.25-0.75mg	Reduced dose	Winkelman JW. Neurology 2006
Ropirinole	0.78-4.6mg	Reduced dose	Allen RP et al. Sleep 2004
Rotigotine	2-3mg	1-3mg	Ortel WF. Sleep Med 2010
Pregabalin (Lyrica) *	150-450mg, 1-2 hours before sleep	Reduced dose	Garcia-Burreguero et al. Sleep. 2018
Gabapentine	800-900mg	200-300mg after each dialysis	
Gabapentin Enacabril (Horizant)	1200mg	Reduced dose	Kushida et al, Neurology 2019
Oxycodone/Naloxone	5mg/2.5mg twice daily up to 40/20 twice daily	May be used in reduced dose. Not recommended if GFR<<15mL/minute	Ortel WF et al. CNS drugs 2016
Intravenous Iron	Ferric Carboxymaltose 1000mg- Ferritin<300ug/l		Allen RP et al. sleep Med 2018 Vaziri ND. Sem Neurol 2016
Vitamine C + E		200mg and 400mg/day/day	Sagheb MM et al Sleep Med 2012
Exercise		30 minute leg stretching and/or 45 minutes cycling during dialysis	Giannaki CD. Nephrology 2013

*Pregabalin causes less augmentation than pramipexole at 52 weeks. Allen RP et al, NEJM 2014;370:2050-2051

Kidney Transplantation and RLS

- Kidney Transplantation improves the symptoms of RLS in a sizeable number of patients (Winkelmann J et al. Mov Disord, 2002)
- Incidence of RLS is as high as 40-50% in patients with kidney transplant failure (Zhang et al. Sleep Sci Med, 2020)
- Kidney transplantation results in significant improvement of uremic neuropathy (Nielsen et al, 1974; Burn et al, 1998; Ho et al, 2012)

Asterixis

- Asterixis is characterized by an inability to maintain sustained posture with brief, shock-like, involuntary movements. This motor disorder is a kind of myoclonus (negative myoclonus) characterized by muscular inhibition rather than contraction.
- Frequency 1-3/sec
- Silent EMG period after asterixis 50-200ms



Ellul et al. Pract Neurol, 2017

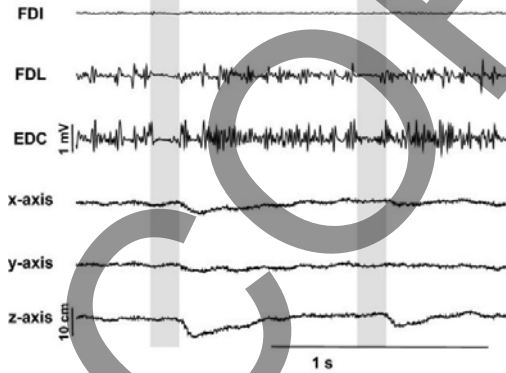
Asterixis

Causes

- Encephalopathies (hepatic, renal hypoxic),
- Electrolyte abnormalities (hypokalemia, hypomagnesaemia)
- Endocrine (hyperparathyroidism)
- Drugs (phenytoin, valproate, carbamazepine, gabapentin, levodopa, opiates, anticholinergics benzodiazepines, lithium, clozapine)
- Viral encephalitis
- Cerebral infarct, hemorrhage, neoplasm

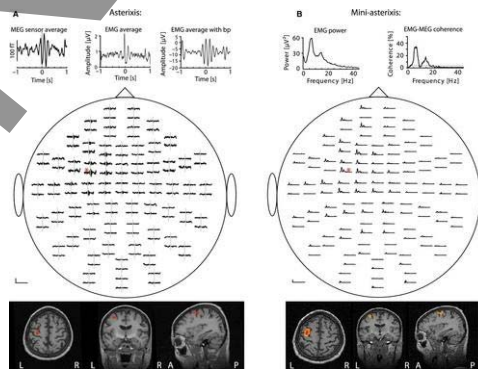
Ellul et al . Pract Neurol. 2017;17:60-62

Physiology



Electromyography shows movements with frequency of 1-3 /second followed by silent periods lasting 50-200 ms corresponding to the loss of muscle tone after asterixis

Asterixis: Pathophysiology Butz et al. Acta Neurol Scan, 2014



Magnetic electroencephalography shows activation of contralateral motor cortex 49ms before asterixis continuing to 99ms after movement.

Chorea

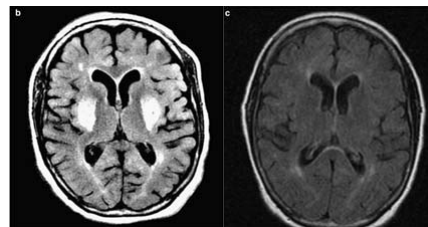
- Chorea refers to involuntary, irregular, purposeless, non-rhythmic, abrupt, rapid, & often un-sustained movements that seem to flow from one body part to another.
- Presence of chorea in CKD is often associated with encephalopathy and MRI abnormalities in basal ganglia.
- Most reported cases of chorea in CKD have concomitant non-ketotic hyperglycemia



Chorea and CKD

- Non-ketotic hyperglycemia is a known cause of acute chorea. Both chorea and basal ganglia abnormalities (reversible edema) disappear after correction of hyperglycemia.

Kirylyuk et al. *Kidney Int* 2008, 73:1087-91



- Left : T2 Flare MRI showing bilateral high signal in basal ganglia
- Right: six weeks later (after correction of non-ketotic hyperglycemia), MRI abnormalities disappeared

Chorea in CKD

Thiamine Deficiency

10 patients with CKD presented with cognitive decline and movement disorders including chorea and dystonia. Mean serum thiamine level was 35.5 nmol/L (normal >50 nmol/L). All patients improved after thiamine replacement

Hung et al. Amer J Kidney Disease
2001;38:941

• Drugs

Famcyclovir
Valacyclovir
Ceftriaxone
Levofloxacin
Levodopa

Myoclonus

- Myoclonus is a hyperkinetic movement disorder characterized by fast (< 50 millisecond duration) jerky movements. It can be focal or generalized
- Anatomically, the site of CNS disturbance in myoclonus can be either cortical or subcortical (basal ganglia or brain stem)
- Severe and frequent myoclonic movements can interfere with rest and sleep and impair quality of life.

Myoclonus in Kidney Disease

Stimulus Sensitive Myoclonus



Mini-myoclonus



Myoclonus in CKD

- Myoclonus in CKD can be cortical or subcortical in origin
- Cortical myoclonus results from metabolic derangement of cortical neurons by CKD. It is usually multifocal, spontaneous, stimulus sensitive or presents as diffuse mini-myoclonus
- The typical stimulus sensitive myoclonus of CKD is believed to be subcortical and due to direct effect of uremic toxins on nucleus gigantocellularis of medulla. In rats, infusion of urea damages and irritates the reticular formation of the medulla and causes stimulus sensitive myoclonus- similar to human stimulus sensitive myoclonus in CKD (Muscatt et al, 1986)
- Medullary myoclonus in CKD is also called reticular reflex myoclonus
- Clonazepam is the drug of choice for treatment of stimulus sensitive myoclonus. In severe cases, it can be given intravenously. Mini-myoclonus usually disappears with improvement of kidney function.
- Ahmad S et al. Expert Rev of Clinical Pharmacol 2019; 12:1, 61-90

Drug Induced Myoclonus in CKD

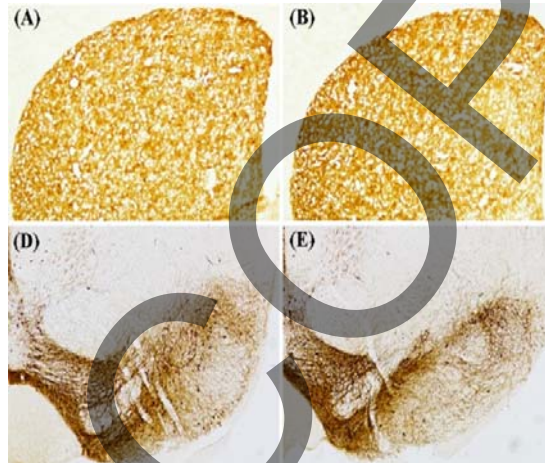
- Drugs with primarily renal clearance when used in CKD can achieve toxic serum levels and cause severe generalized myoclonus
- Drug induced myoclonus can be spontaneous or stimulus induced. Frequent myoclonic jerks can impair patients' consciousness and lead to coma.
- Gabapentin, pregabalin, carbamazepine, lithium, metoclopramide, acyclovir, opioids, flecainide, debutamine, dexamethasone are mostly implicated.
- In a recent review of the literature on 50 patients with gabapentin and pregabalin induced myoclonus, 88% of the patients had CKD (Desai et al, 2018).

Action Myoclonus Renal Failure Syndrome (AMRF- Andermann syndrome)

- Described first in French - Canadian population, affected patients start with tremor, myoclonus and ataxia in the 2nd and 3rd decade of life.
- Renal failure is progressive. Renal biopsy shows collapsing glomerulopathy, a severe variant of segmental glomerulosclerosis.
- Brain pathology: loss of cerebellar granular cells.
- AMRF syndrome is caused by deletion/duplication of scarb2 gene.
- Renal failure improves with dialysis. Myoclonus responds to clonazepam.
- Berkovic et al; Brain 2004: 127:2173-2182

Parkinsonism: Bradykinesia, Hypokinesia, Tremor

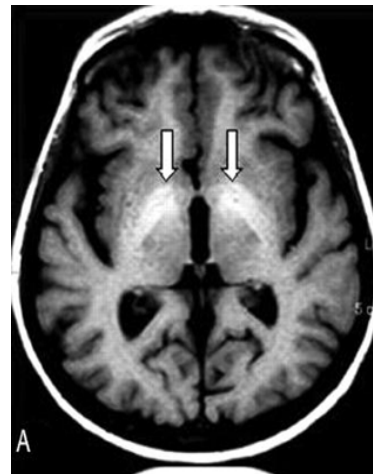
- Paucity and slowness of movement is uncommon in CKD and probably reflect multiple factors including metabolic encephalopathy, vitamin deficiency, medication effect, etc
- True Parkinsonism is very uncommon, suggesting that brain dopamine is not significantly depleted in CKD.



In adenine rich diet mice model of CKD, tyrosine hydroxylase staining of striatum shows similar findings between striatum of mice with CKD and control mice.
Mazumder et al 2019

MRI Abnormalities in CKD without NKH Associated with High Serum Magnesium Level

- 10 patients with CKD and hemodialysis of more than 2 years
- All had increased serum magnesium level
- Two had parkinsonism
- Distinct MRI abnormalities were evident in a patient with parkinsonism and second highest magnesium level (1.18 ng/mL)
- da Silva et al. AJNR 2007;28:1479



MRI of a patient with CKD, Parkinsonism and increased serum magnesium: Bilaterally increased high signals are present in the T1 image

Conclusions

- RLS needs aggressive treatment since it is associated with increased mortality in CKD
- Chorea is often associated with non-ketotic-hyperglycemia, less often with thiamine deficiency, infarct or hemorrhage in BG
- Myoclonus and asterixis are usually associated with encephalopathy – Myoclonus responds well to clonazepam, asterixis does not need treatment.
- Parkinsonism is rare in CKD (possibly related to high manganese levels in basal ganglia?)

Movement disorder	Location of pathology
RLS	Hypothalamus ?
Chorea	putamen, globus pallidus
Myoclonus	Medulla , cortex
Asterixis	cortex
Parkinsonism	Putamen