CHILDREN'S
HOSPITAL OF RICHMOND AT VCU

Nephrology Issues with Connective Tissue Disorders & Mitochondrial Disorders

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Disclosure

* Nothing to Disclose

Goals and Objectives

* 1. what are the kidney manifestations of mitochondrial diseases ?
* 2. when the kidneys are involved how does that effect the blood pressure, electrolytes, urine out put?
* 3. what can be done to minimize these issues

Systemic Lupus Erythematosus

* Brain and head involvement
* Heart and lung and liver involvement
* Gut motility and inflammation involvement
* Kidney involvement
* Joint involvement
* Fatigue, fevers, blood pressure changes
* Electrolyte (lab) changes

Systemic Lupus Erythematosus

* A relative easy disease to identify and treat for
  * It can be identified by clinical and lab criteria
  * It can be monitored by clinical and lab criteria
  * It can be placed into remission and monitored by clinical and lab criteria

Mitochondrial Diseases

* Brain and head involvement
* Heart and lung and liver involvement
* Gut motility and inflammation involvement
* Kidney involvement
* Joint involvement
* Fatigue, fevers, blood pressure changes
* Electrolyte (lab) changes

Affected system	Manifestations
Neurological	Apnea, hypotonia, lethargy, developmental delay, psychomotor regression, ataxia, stroke-like episodes, hemiparesis, spasticity, seizures, dementia, leukodystrophy, myoclonus, cortical blindness, migraine, polyneuropathy (sensory and/or motor), neurogenic bladder
Muscular	Myopathy, hypotonia, exercise intolerance
Hearing	Hearing loss
Cardiac	Cardiomyopathy, arrhythmias, heart block
Renal	Proximal tubulopathy, De Toni-Debré-Fanconi syndrome, proximal tubular acidosis, Bartter-like tubulopathy, hypermagnesuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, myoglobinuria, renal failure
Endocrine	Diabetes mellitus, hypoparathyroidism, hypothyroidism, hyporeninemic hypoaldosteronism, growth hormone deficiency
Gastrointestinal	Liver dysfunction, hepatomegaly, liver failure, vomiting, diarrhea, malabsorption, pseudoobstruction, intestinal dysmotility, exogenous pancreatic insufficiency
Hematological	Sideroblastic anemia, neutropenia, thrombocytopenia
Ocular	Progressive external ophtalmoplegia, ophtalmoparesis, pigmentary retinal degeneration, ptosis, cataract, optic atrophy, blindness
Antenatal symptoms	Dysmorphic features, malformations, intrauterine growth retardation polyhydramnios
Cutaneous	Mottled pigmentation, discoloration, acrocyanosis, vitiligo, cutis marmorata, anhydrosis and jaundice, hyperhidrosis, trichothiodystrophy, hirsutism alopecia, alopecia with brittle hair, symmetric cervical lipomas

Emma F et al, Pediatric Nephrology 2012, 27: 539-550

Mitochondrial Diseases

* A difficult disease to treat for
  * It is difficult to identify by clinical and lab criteria
  * No hard lab data exists making it a clinical decision making based upon patient and medical provider experience
  * Just when you think you are effecting one issue another arises

Kidney disease in General

* Glomerular
  * IDDM, HTN, Chronic Glomerulonephritis
    * Associated with salt and water retention, edema and hypertension
* Tubular interstitial
  * Cystic dysplasia, hypoplasia
    * In most children this is congenital
    * Associated with an inability to conserve water and sodium

Tubular interstitial

* Clinically these patients are polyuric (pee like a race horse) and polydipsic (drink like a fish)
  * Urine specific gravity may not show the ability to concentrate the urine with a specific gravity usually of 1.010. A chronic low specific gravity may be misinterpreted as a well hydrated patient
* This predisposes to be chronically “dry”

Tubular interstitial

* 48 hours ago a 15 yr old showed up to our ED with a 2-3 liter urine out put
* With no hypertension
  * Cr 9.9 mg/dl (2 percent kidney function)
  * K of 6.4 meq/dl
  * Ca of 4.0 mg/dl

So why?

* Does my child/patient seem always dehydrated?
* Kidneys are in an oxygen enriched environment that is metabolically very active
* Renal involvement in Mitochondrial disease are associated with TIN (tubular interstitial nephritis)
* Like congenitally acquired renal disease this is associated with polyuria and polydipsia

So why?

* Does my child/patient have problems with urine out put?
  * Bladder dysfunction is in part a frequent finding in these children
  * Bladder muscle dissociation
  * A variation of “Hinman” syndrome
    * Non-neurogenic, neurogenic bladder

So why?

* Bladder dissociation
  * A lack of coordination of detrusor muscles of the bladder
  * Often results in urinary retention
  * Added comorbidity of this is related to bowel dysfunction
    * This is similar to what is seen in “prune belly syndrome” also called Eagle-Barrett syndrome

So why?

* Does my child/patient have electrolyte disorders?
* Renal biopsies performed in children with Mitochondrial disease demonstrate interstitial scarring. This is not associated with hypertension nor "active" urinary sediment but associated with Na, K, HCO3, Mg, Ca, Phosphorous (phos) and water wasting

So why?

* Does my child/patient have electrolyte disorders?
* Wasting of Na results in volume depletion
* Interstitial nephritis results in K, Phos and HCO_3 wasting with associated hypokalemia, hypophosphatemia and metabolic acidosis
* Calcium and Mg wasting may have variable effect of wasting

So why?

* Does my child/patient have electrolyte disorders?
* Many of these patients will be on medications that are associated with electrolyte wasting
  * E.g. Topamax, Depakote,
* Hypo Mg, hypo K and hypo Phos may result in muscle weakness adding to risk of ***Rhabdomyolysis***

So why?

* Does my child/patient have chronic renal failure associated with mitochondrial disorders?
* Signs and symptoms of CKD are subtle
* Serum creatinine may be normal despite diminished renal function due to poor muscle mass

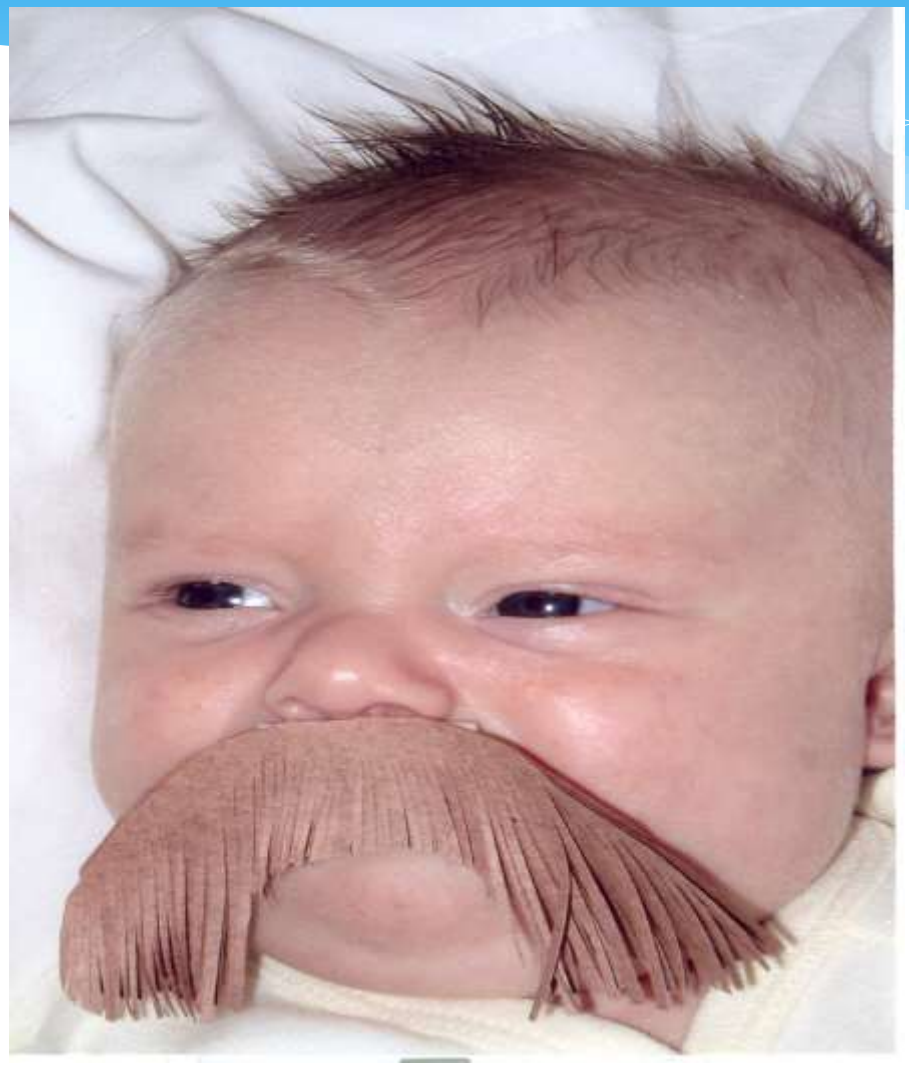
So why?

* Does my child/patient have blood pressure instability?
* Orthostatic hypotension (old term) is a phenomena of getting dizzying or passing out when one stands up in a hurry often with associated tachycardia
* If one is “dry” and develops tachycardia then the filling volume is diminished due to lack of filling time

So why?

* Does my child/patient have blood pressure instability?
* Etiology in Mitochondrial disease patients is multifactorial
  * Volume depletion due to the tubular interstitial renal disease with associated dehydration
  * Electrolyte disturbances
  * Cardiac dysfunction
  * “autonomic” dysfunction

So what can we do about these issues?



Kidney involvement in Mitochondrial diseases

* Affecting the underlying disease
* Tubular interstitial disease
  * Avoid other nephrotoxins
    * Eg NSAIDs
* Electrolyte disturbances
  * Beware of other meds that cause tubular wasting and monitor appropriately
    * Serum phos is not on any of the pre set blood panels

Kidney involvement in Mitochondrial diseases

* Bladder dysfunction
  * Time voiding, may need CIC, consider terazosin (alpha blocker that decreases sphincter tone)
* Orthostatic hypotension
  * Volume repletion
  * Salt loading
  * Short acting B Blocker for tachycardia

Summary

* Like all other aspects of Mitochondrial disease the kidney involvement is variable and may be subtle
* Diagnosis of kidney involvement may be done but
  * Blood work
  * Kidney imaging (suggestive not diagnostic)
  * Kidney biopsy

Conclusive

* Children and adults with Mitochondrial disease require a coordinated care team that communicates within and understands and appreciates the subtlety of this rare disease
* Families need to help educate medical care givers on the nuances of this rare disease