SICKLE CELL DISEASE AND THE PAEDIATRIC KIDNEY

– *The Sickle Cell Unit Experience*

Sickle Cell Unit
UWI, Jamaica

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Objectives

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- Overview Sickle Cell Nephropathy
- Review paediatric renal research from SCU

Sickle Cell Disease

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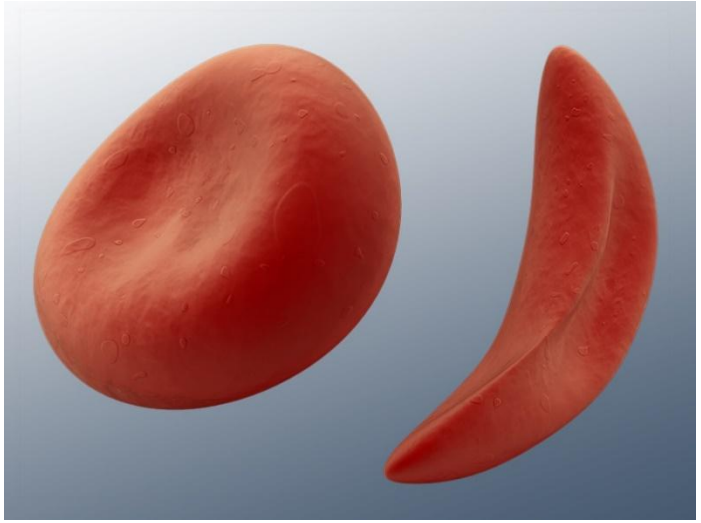
- Group of inherited red cell disorders
  - One of most common monogenic disorders worldwide
- Characterized by haemolysis, vaso-occlusion and inflammation
- Multisystem disorder which may be severe with:
  - Acute episodes such as painful crises, acute chest syndrome, stroke
  - Progressive organ damage: renal, cardiac, hepatic



SCD Pathophysiology

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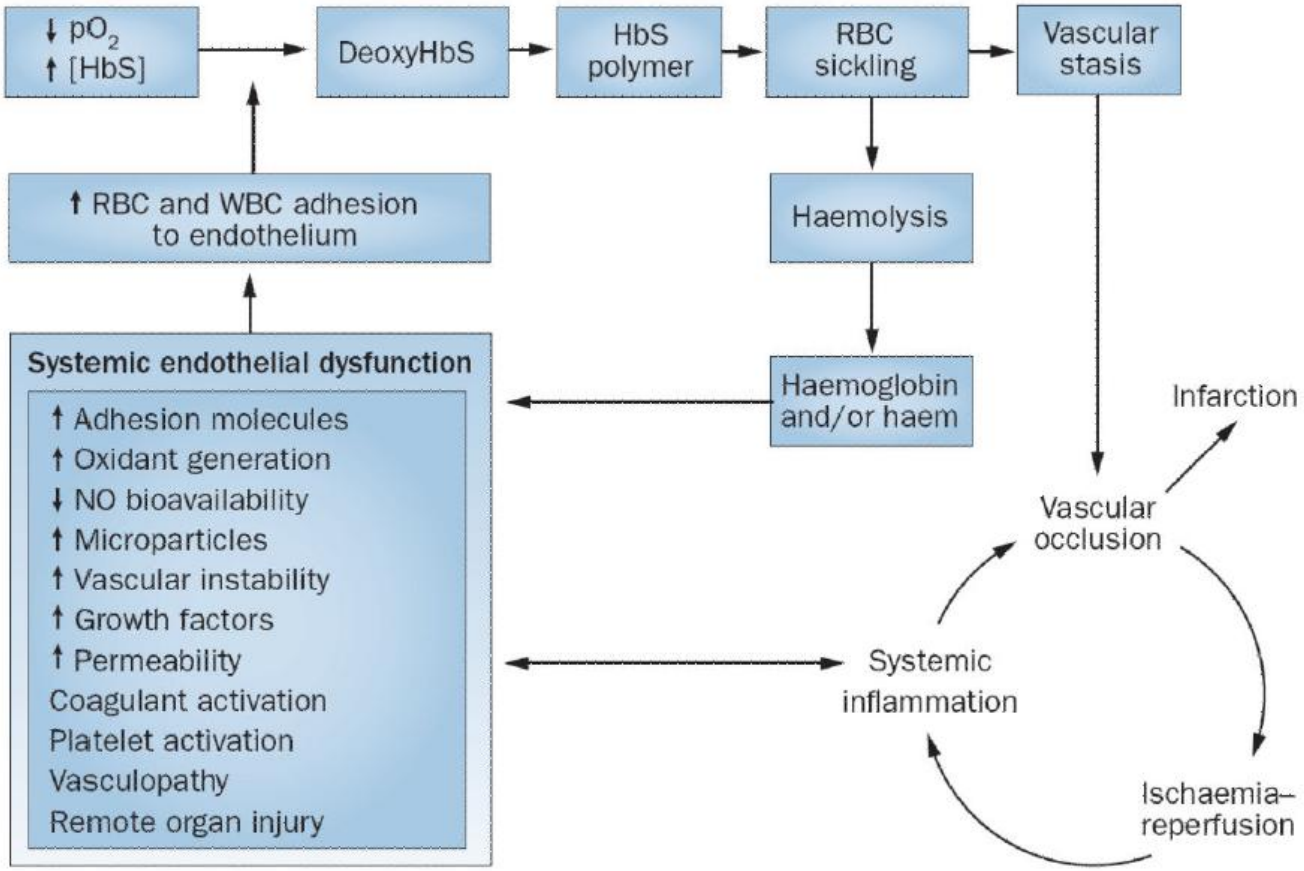

Nath KA, Hebbel RP. Nature Review Nephrology 2015; 11: 161-171

SCD & Kidney

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- SCD adversely affects all major physiological processes in kidney → complications:
  - Common & chronic: impaired concentration ability
  - Rare & fatal: renal medullary carcinoma
- Renal involvement can occur throughout the lifespan of a person with SCD
  - Infancy: hyperfiltration, hypertrophy & impaired concentration ability
  - Childhood: Microalbuminuria / Nephrotic syndrome
  - At any age: haematuria & acute kidney injury
  - Early to middle adulthood: Macroalbuminuria ±regression in GFR
  - Later decades: CKD, further reduction in GFR, ESRD
- Age dependent accrual of kidney disease contributes substantially to the still increased mortality in SCD

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SCD & Kidney

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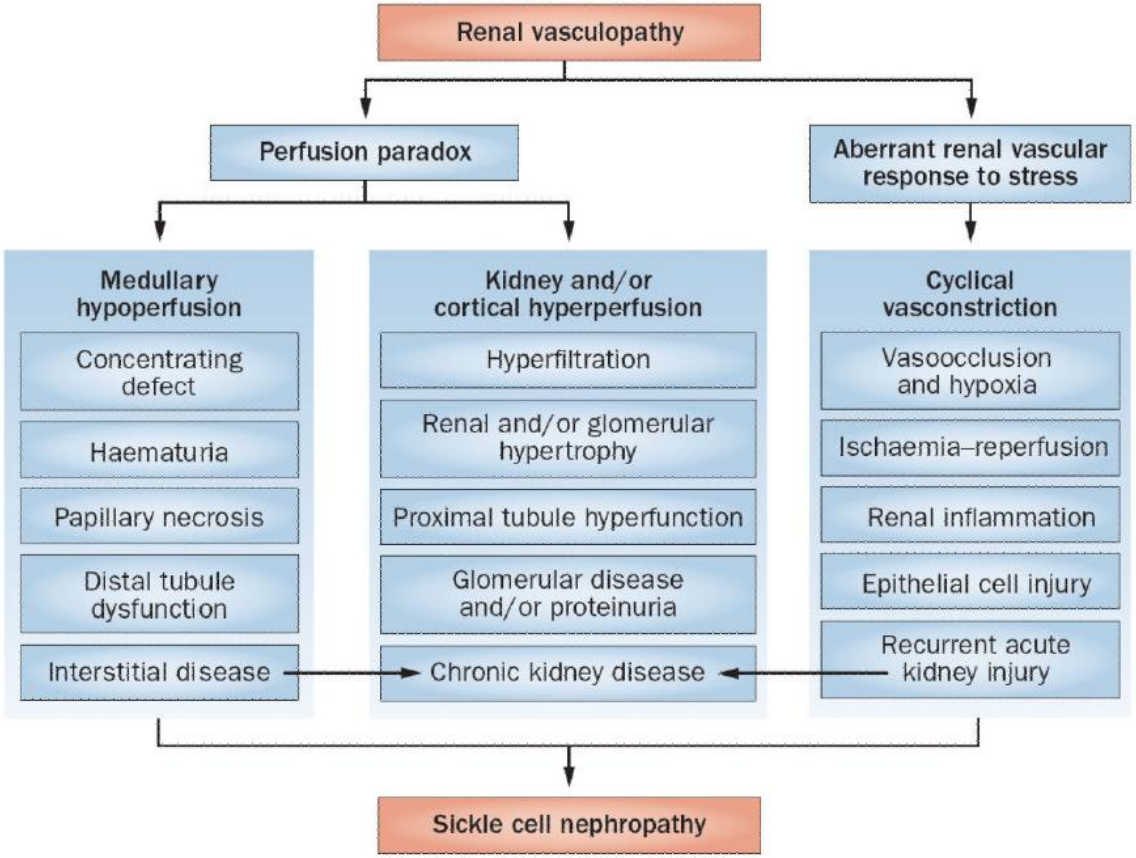

SCN Nephropathy

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- Most common pathology: Focal segmental glomerulosclerosis
- Proteinuria is age dependent
  - Natural progression
  - Associated factors eg: ↑BP, low Hb, parvovirus B19
- An important cause of morbidity and mortality
  - ~18% of deaths in Jamaican with SS over 20 years of age.
  - Jamaica: 6% CKD≥ Stage 3 by mid-30s
- **Early detection CRITICAL**

SCU RESEARCH

Nocturnal Enuresis in Hb SS - Prevalence

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- Patients (JSCCS); age 8 years
  - 175 Hb SS
  - 106 Hb SC
  - 150 Hb AA
- Enuresis

Prevalence	Boys (%)	Girls (%)
Hb SS	52	38
Hb SC	10	20
Hb AA	22	20

Readett DRJ et al. Archives of Disease in Childhood 1990; 65: 290-3

Nocturnal Enuresis in Hb SS - Determinants

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- Patients (JSCCS)
  - 16 Hb SS (enuretic nightly); age 8 – 13 years
  - 16 Hb AA (non-enuretic); age 8 – 13 years
- Overnight admission
  - Fluid deprivation test (no ADH)
  - Maximum functional bladder capacity measurement
- Results
  - No significant difference in maximum urine osmolality / urine volumes

Readett DRJ et al. Archives of Disease in Childhood 1990; 65: 615-618

Nocturnal Enuresis in Hb SS - Determinant

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- Results
  - Maximum functional bladder capacity lower in enuretic group
  - Overnight urine volume: maximum functional bladder capacity higher in enuretic group
  - Subjective analysis: enuretic group more likely to be considered deep sleepers
- Conclusions
  - Nocturnal enuresis not simply a reflection of defect in conc. ability & higher urinary volumes
  - Treatment should focus on converting enuresis to nocturia

Readett DRJ et al. Archives of Disease in Childhood 1990; 65: 615-618

Renal Lengths in SCD

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- Subset from Jamaica Sickle Cell Cohort study
  - 237 Hb SS; 147 Hb SC; 78 Hb AA controls
- Age range
  - SCD: 6 – 20 years
  - Hb AA: 15 – 19 years
- Ultrasound study
- Results
  - Renal lengths increased with age in all genotypes
  - Mean length: SS > SC > AA
  - Higher renal lengths associated with lower Hb, high retic

Walker T.M et al. Clinical Nephrology 1996; 46: 384-388

Microalbuminuria

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- Aim: To determine prevalence & predictors of MA
- Participants
  - 244 children, Hb SS
  - Mean age: 7.2 years (2.0 – 13.8 years)
- Results
  - 45 children (18.6%) with MA
  - Mean age 7.8 years
    - Youngest child 2.8 years
  - ACR: 32 – 260 µg/mg

King L et al. Archives of Disease in Childhood 2011: 96: 1135-39

Microalbuminuria

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- Results: Univariable regression model

Variable	Coefficient	P-value	Lower 95% CI	Upper 95% CI
Glomerular hyperfiltration	0.60	<0.001	0.26	0.94
Dactylitis	0.44	< 0.02	0.08	0.80
Age	0.07	0.02	0.01	0.12
Hb	- 0.18	< 0.03	- 0.34	- 0.02
Hb F	- 0.03	< 0.04	- 0.05	- 0.003
eGFR	0.01	< 0.001	0.005	0.02
BMI	- 0.01	0.07	- 0.22	0.0008
LDH	0.4	0.06	- 0.01	0.8

Microalbuminuria

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- Results: Multivariable regression model

Variable	Coefficient	P-value	Lower 95% CI	Upper 95% CI
Male sex	- 0.02	0.9	- 0.36	0.31
Age	0.08	0.01	0.02	0.15
eGFR	0.01	0.03	0.001	0.01
BMI	- 0.16	0.02	- 0.28	- 0.03

King L et al. Archives of Disease in Childhood 2011: 96: 1135-39

Microalbuminuria

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- Lessons
  - MA was detected as early as 2.8 years
  - MA was associated with dactylitis and higher eGFR supporting the contribution of ishaemia and hyperfiltration to the pathogenesis of renal disease

Glomerular Disease & Outcome

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- Aim: To determine renal histology and outcome in children presenting with glomerular disease
- Participants
  - 19 Hb SS
  - Mean age 8.3 years (4.6 - 10.8 years)
- Biopsy Indication
  - Nephrotic syndrome (n=13)
  - GN atypical for PSGN (n=4)
  - Unexplained proteinuria (n=1)
  - SLE staging (n=1)

Miller M, et al. Unpublished

Glomerular Disease & Outcome

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Table 1 Variation of histology with age in children with homozygous sickle cell disease

Histology	Number	Mean ±SD	Range
DPGN	7	7.7 ± 2.3	5 – 10.5
MesPGN	7	8.6 ± 2.3	5.8 – 12
MPGN I	3	9.5 ± 1.3	8.3-10.8
MCD	1	4.6	
FSGS	1	10.1	
Total	19	8.3 ± 2.2	4.6 – 12

DPGN diffuse proliferative glomerulonephritis, *MesPGN* mesangial proliferative glomerulonephritis, *MPGN I* membranoproliferative glomerulonephritis type I, *MCD* minimal change disease, *FSGS* focal segmental glomerulosclerosis

Glomerular Disease & Outcome

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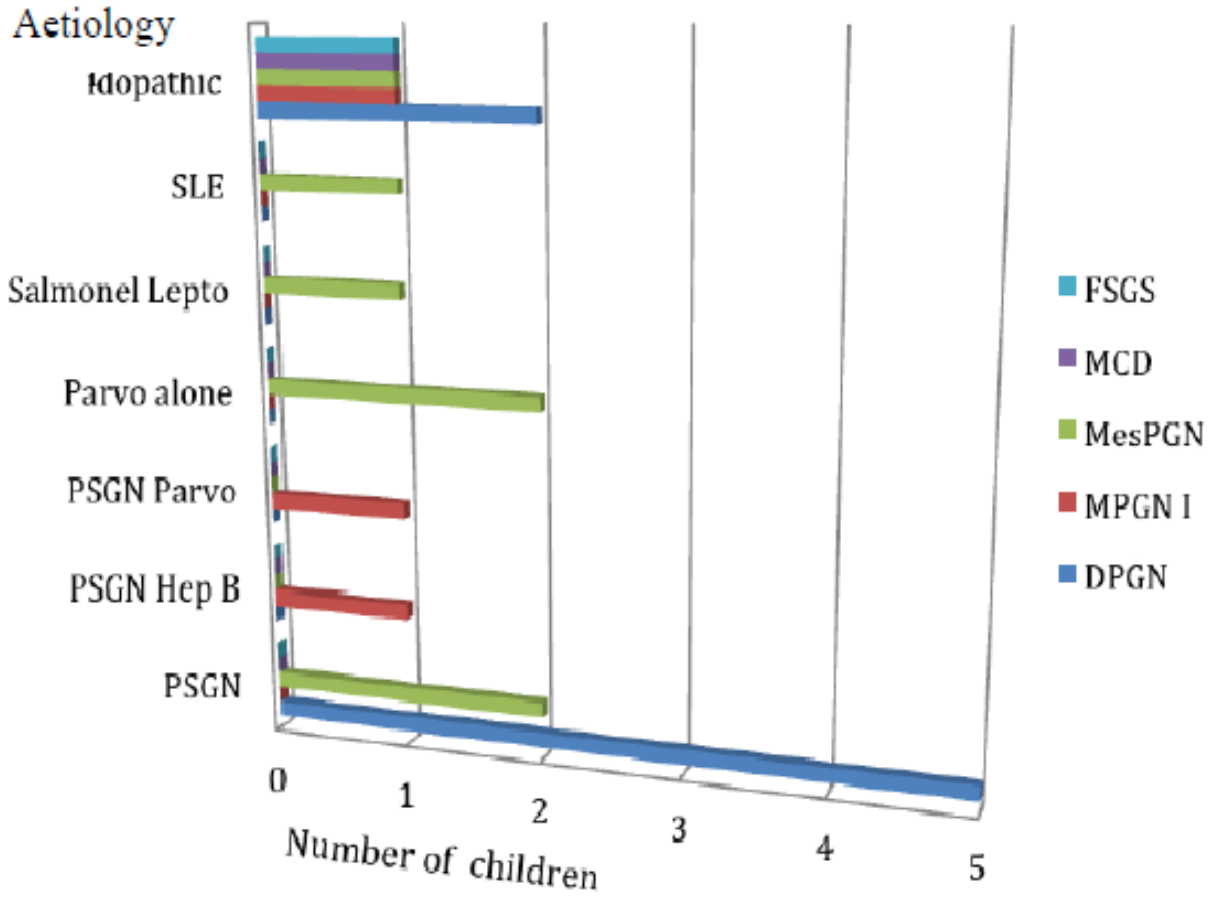

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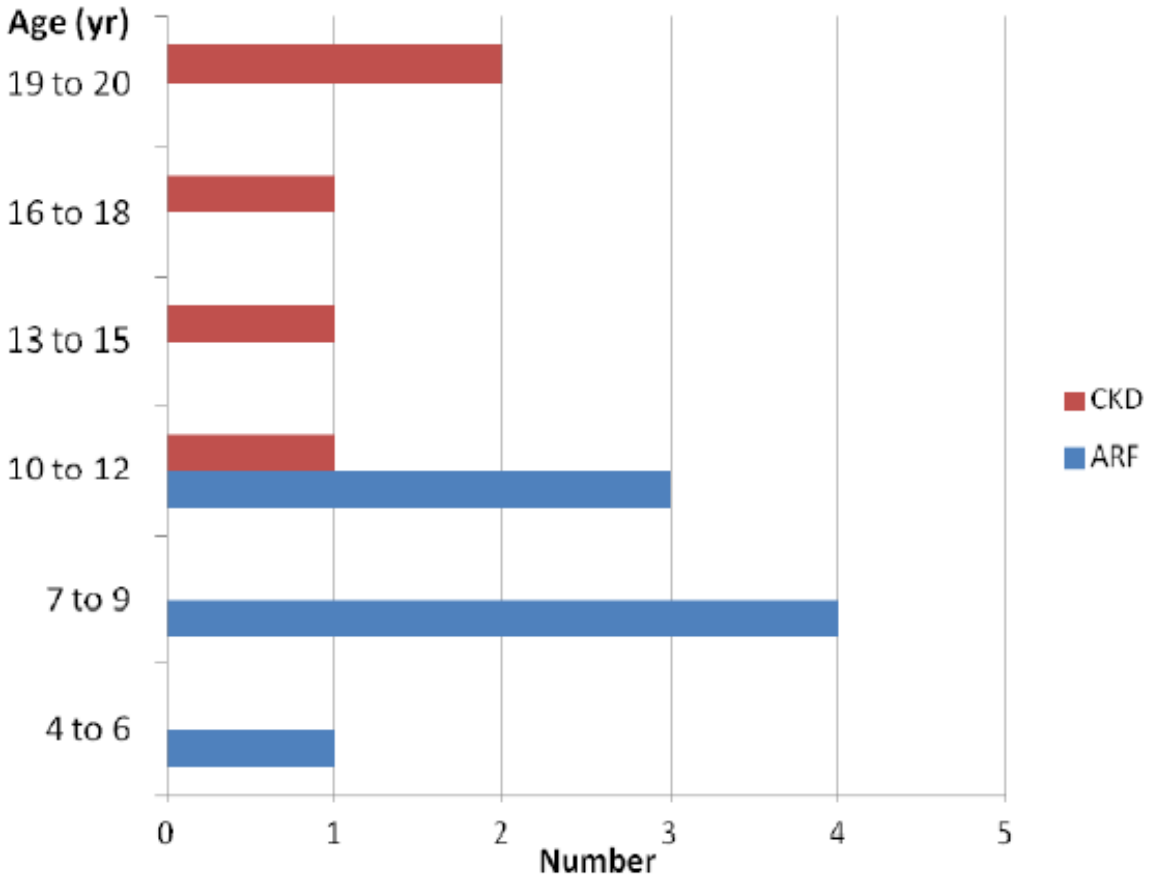

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Glomerular Disease & Outcome

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- Lessons:
  - Glomerular disease in children with SCD < 12 years is not necessarily reflective of "sickle cell nephropathy"
  - SCD children with renal disease should undergo full evaluation and treatment based on clinical, serological and histological parameters.

Miller M, et al. Unpublished

Summary

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- SCD alters renal structure and function from an early age, contributing to the development of SCN
- Early detection of renal disease is CRITICAL
- Appropriate interventions tailored to individuals renal manifestations should be employed
  - MA: ACEi & HU
- SCN increasing burden with advanced age

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Thank you