ARTHROPATHIC CHANGES IN PATIENTS WITH INFANTILE NEPHROPATHIC CYSTINOSIS – IS THERE A GENETIC ASSOCIATION?

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BACKGROUND

- Cystinosis is a rare autosomal recessive disorder affecting 1:175,000.
- The most severe form of the disease, infantile nephropathic cystinosis, accounts for 95% of cases, with features appearing between 6-12 months of age.
- Cystinosis is caused by mutations in the *CTNS* gene, mapped to chromosome 17p13[1].
- The gene encodes the lysosomal membrane co-transporter cystinosin, mutations in which lead to the accumulation of intralysosomal cystine[2].
- Cystine deposition leads to progressive multisystemic disease including proximal tubular dysfunction.
- If untreated, end-stage renal disease (ESRD) can occur by 10 years.
- The mainstay of management is the drug cysteamine. It has been demonstrated to improve growth and prolong time to ESRD[3].

OBJECTIVES

- We describe 3 unrelated patients with infantile nephropathic cystinosis residing within a small region of the West of Scotland. All 3 demonstrate significant growth failure and joint pathology, presumably secondary to cystinosis.
- We aim to investigate whether there is a clear genetic basis to these arthropathic changes.

CASES

- The joint changes observed range from severe, symmetrical arthropathy of the femoral heads (Case 1) to chronic, recurrent multifocal osteomyelitis (Case 2), and early metaphyseal cupping and splaying despite adequate vitamin D replacement (Case 3).
- All patients had 2 mutations in the *CTNS* gene with some inter-individual overlap between mutations observed.
- All 4 mutations have been reported in association with cystinosis within European cohorts but none have been linked to arthropathy[4,5].
- ***Figure 1*** displays the radiographic features of these patients.
- ***Table 1*** summarises the patients' clinical and biochemical features, along with their genetics.

CONCLUSIONS

- Infantile nephropathic cystinosis leads to a degree of growth failure due to multifactorial causes including renal osteodystrophy, hypophosphataemia, proteinuria and nutritional deficiency.
- These 3 cases expand on this phenotype and demonstrate destructive and progressive joint involvement alongside the commonly observed features of short stature and osteopenia.
- Our data suggests that there may not be a single *CTNS* gene mutation responsible for the development of arthropathy in cystinosis.
- Further research is required to look at the association between cystinosis and arthropathy and to ascertain whether there is a predictable genetic component to this, or whether other factors may play a role. Understanding this link would allow surveillance of patients at risk of arthropathy, and early management of joint problems could help improve quality of life for these individuals.

Figure 1

Case 1: ***Figure 1A*** – XR lateral left knee; severe arthritic change. ***Figure 1B*** – XR AP left tibia/fibula; healed left tibial osteotomy, marked osteopenia, left tibiofemoral and tibiotalar arthritic change.

Case 2: ***Figure 2A*** – XR AP left knee; osteopenia, joint surface irregularity, chondrocalcinosis. ***Figure 2B*** – XR leg length; marked genu valgum, rotated pelvis, hip joint arthritis. ***Figure 2C*** – XR AP pelvis; osteopenia, bilateral hip joint narrowing, left femoral head erosions. ***Figure 2D*** – MRI coronal T1 pelvis; bilateral hip joint narrowing and femoral head erosions. ***Figure 2E*** – CT coronal pelvis; bilateral hip joint narrowing and femoral head erosions. ***Figure 2F*** – XR lateral lumbar spine; osteopenia, mild kyphosis, L2 central compression fracture. ***Figure 2G*** – XR AP left hand; osteopenia, marked CMC joint space loss, carpal bone (especially scaphoid) erosions.

Case 3: ***Figure 3A*** – XR AP left hand; metaphyseal cupping and sclerosis.

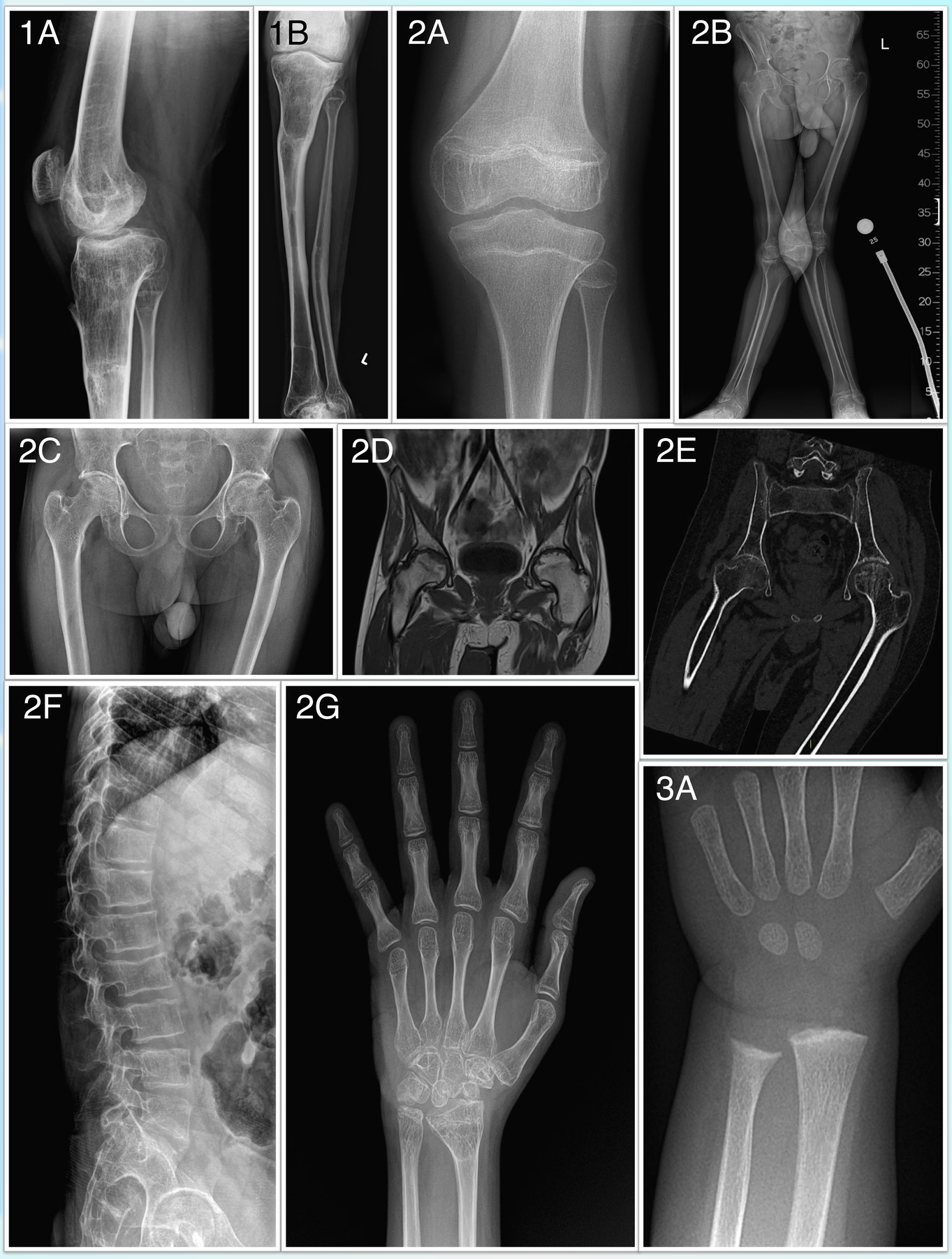

Table 1

	Case 1	Case 2	Case 3
eGFR – at diagnosis	25.2	119.1	32.7
eGFR – current	66.5	114	41.5
Leucocyte cystine levels – at diagnosis (nmol half-cystine/mg protein)	2.84	0.48	1.33
Leucocyte cystine levels – current (nmol half-cystine/mg protein)	1.91	0.76	0.72
Height (Z-score)	-5.05	-7.66	-2.6
Genetics	Compound heterozygote for c.922G>A mutation and recurrent 57kb deletion	Compound heterozygote for c.473T>C and c.561+1del mutations	Compound heterozygote for c.473T>C mutation and recurrent 57kb deletion
DEXA scan results (T-score)	Lumbar spine: -2.1 Hips: -2.4	Total: -2.0	N/A
Age of diagnosis of arthropathy (years)	10	6	2
Joints involved	Hip, knee, metacarpal and metacarpophalangeal	Hip, intervertebral	Wrist

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