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Original article

Renal disease in Cockayne syndrome

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ABSTRACT

Background: Cockayne Syndrome (CS) is a rare autosomal recessive multi-systemic disorder, characterized; by developmental delay, microcephaly, severe growth failure and sensorial impairment. Renal complications have been reported but remain underinvestigated. The objective of this study was to perform a review of renal disease in a cohort of CS patients.

Methods: We retrospectively collected relevant clinical, biochemical and genetic data from a cohort of 136 genetically confirmed CS patients. Blood pressure (BP), proteinuria, albuminemia, uric acid, creatinine clearance, renal ultrasounds and renal biopsy result were analysed.

Results: Thirty-two patients had a renal investigation. We found that 69% of investigated patients had a renal disorder and/or an elevated BP. Fifteen out of 21 patients (71% of investigated patients) had an increased BP, 10 out of 16 patients (62% of investigated patients) presented with proteinuria and 4 of them had a nephrotic syndrome. Thirteen patients out of 29 (45%) had a decreased Glomerular Filtration Rate (GFR), 18 out of 25 patients (72%) had a hyperuricemia. No correlation with the genetic background or clinical types of CS was found, except for the renal clearance.

Conclusions: Renal disease, increased blood pressure and hyperuricemia were highly prevalent in our study. We believe that CS patients should benefit from a nephrological follow-up and that anti-uric acid drug and Angiotensin-converting enzyme (ACE) inhibitor should be discussed in these patients.

1. Introduction

Cockayne Syndrome (CS) is a rare autosomal recessive multi-systemic disease which was first described by E. Cockayne in 1936 (Cockayne, 1946). The incidence of genetically confirmed CS is 2.7 per million livebirths in Western Europe (Kleijer et al., 2008). CS is caused by defects in DNA repair and belongs more specifically to the family of nucleotide excision repair disorders, together with xeroderma pigmentosum and trichothiodystrophy. CS is characterized by progressive cachectic dwarfism with developmental delay, microcephaly, sensorial impairment (progressive hearing loss, pigmentary retinopathy, cataracts and enophthalmia), cutaneous photosensitivity, dental decay and recognizable facial appearance with deep sunken eyes and progeroid features (Laugel, 2013; Nance and Berry, 1992).

Several clinical types of CS exist depending on the age at onset and severity. These subtypes constitute a clinical continuum between a severe congenital form or early-onset CS (CS type II), in which patients usually die before the first decade of life, and a mild juvenile form or late-onset CS (CS type III), in which patients usually survive until adulthood and include the classical infantile form (CS type I) in which patients develop the symptoms in the first two years of life and have a life expectancy of approximately 16 years (Gitiaux et al., 2015; Laugel, 1993, 2013). Mild patients presenting with only a UV-sensitive syndrome and very severe patients with Cerebro-oculo-facio-skeletal syndrome (COFS), characterized by congenital neurogenic arthrogryposis, microcephaly, microphtalmia and cataracts, were also found to share

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the same genetic background and further widen this spectrum (Laugel et al., 2008). In a retrospective study including 45 CS patients, 31% of patients had a severe form (CS type II/early-onset CS), 36% had a moderate form (CS type I/classical CS), 33% had a mild form (Type III/mild form) (Natale, 2011).

The diagnosis can be confirmed by the presence of a defective recovery of RNA synthesis in fibroblasts after ultra-violet light exposure (Mayne and Lehmann, 1982; Schmickel et al., 1977). Most cases of CS are caused by mutations in two genes: *ERCC6/CSB* (Cockayne Syndrome B) and *ERCC8/CSA* (Cockayne Syndrome A), which have been identified in 1992 and 1995, respectively (Henning et al., 1995; Troelstra et al., 1992).

Renal complications have been reported, but remain under-investigated in CS patients and only limited data on renal impairment among CS patients are available. The first case of renal involvement in CS was reported in 1966 by Ohno and Hirooka, (1966). Based on various reports, hypertension and moderate to nephrotic proteinuria can be found in CS patients. Kubota et al. showed that renal failure has a very important influence on the prognosis for CS patients (Kubota et al., 2015). The physiopathology of renal impairment remains incompletely elucidated, however nephron reduction, arteriolosclerosis, glomerular hyalinosis have been reported and can be linked with the accelerated ageing process (Forsythe et al., 2009; Funaki et al., 2006; Higginbottom et al., 1979; Hirooka et al., 1988; Reiss et al., 1996; Sato et al., 1988).

Hence, in order to better describe the renal disease in CS patients, we performed a retrospective study, on a cohort of 136 CS patients and further investigated 32 CS patients in this cohort for whom detailed renal data were available.

2. Patients data and methods

2.1. Data collection

Data were collected in a genetic laboratory database including clinical, biochemical and genetic information of 136 genetically confirmed CS patients (from 23 countries). 52 patients (38%) were classified as CS type I, 27 (20%) as CS type II, 8 (6%) as CSIII, 6 (4%) as COFS, and only 1 patient (1%) had an UV-sensitive syndrome. Three patients (2%) had a combined form XP-CS. For the other 39 patients (29%) no enough data were available or phenotype was atypical and classification in subtypes was not possible.

We retrospectively included 32 CS patients with renal data available with a confirmed diagnosis of CS and documented CSA/CSB mutations (Calmels et al., 2016; Bloch-Zupan et al., 2013; Laugel et al., 2010). Blood pressure, proteinuria, uric acid, creatinine clearance, renal ultrasound and renal biopsy results were retrospectively retrieved from the records.

The study received a formal approval from the Local Ethics Committee (Programme Hospitalier de Recherche Clinique N°3658). Informed consent was obtained from the parents of patients prior to the study.

2.2. Patients' characteristics

We included 32 patients (13 girls, 19 boys), with a mean age of 8 ± 7 years (1–31 years) at the time when the renal clinicobiological assessment was performed. Causative genetic mutations were found in CSA in 13 patients (41%) and CSB in 19 patients (59%). 18 patients were described as having CS type I (57%), 9 type II (28%), 2 type III (6%) and 3 with COFS (9%). Mean weight-for age standard deviation score (SDS) was under the 3rd percentile and mean height-for age SDS was under the 5th percentile. Eleven children have died since their participation in the clinical research program, i.e. 34% patients. The mean age of death was 11 ± 11 years (2–32 years). Among these patients 2 were classified as COFS, 6 as CS type II, 2 as type I, and one patient as type III.

2.3. Blood pressure measurement

We calculated systolic blood pressure (SBP) and diastolic blood pressure (DBP) SDS for each child according to the fourth report of the National High Blood Pressure Education Program. Hypertension was defined as SBP and/or DBP above the 95th percentile for sex, age and height percentile (according to the Pediatric BP Task force Report), as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg for patients older than 18 years (2 patients).

Stage 1 hypertension was defined as BP levels that range between the 95th and the 99th percentile +5 mmHg and stage 2 hypertension as BP levels that range above the 99th percentile +5 mmHg (National High Blood Pressure Education Program Working Group on High Blood Pressure in and Adolescents, 2004).

2.4. Biological assessments

Hypoalbuminemia was defined as an albuminemia lower than 30 g/L. Proteinuria was considered significant when total urine protein level exceeded 300 mg/day or spot urine exceeded 30 mg/dl, according to KDOQI guidelines. Nephrotic syndrome was defined as the association of hypoalbuminemia below 30 g/L with proteinuria greater than 50 mg/kg/day (National Kidney, 2002).

The Schwartz modified equation was used to estimate Glomerular Filtration Rate (GFR) of patients, as follows: estimated GFR (mL/min/1.73 m^2) = 0.413 x (Height/Serum Creatinine) with height in centimeters and serum creatinine in mg/dL (Schwartz et al., 2009). According to KDOQI guidelines, stage 1 of chronic kidney disease (CKD) was defined as GFR > 90 mL/min/1.73 m^2 with kidney damages, stage 2 as GFR between 60 and 89 mL/min/1.73 m^2, stage 3 as GFR between 30 and 59 mL/min/1.73 m^2, stage 4 as GFR between 15 and 29 mL/min/1.73 m^2 and stage 5 as GFR < 15 mL/min/1.73 m^2 (National Kidney, 2002).

Uric acid was considered increased when above 210 µmol/L in infants, 320 µmol/L in children older than 12 years and 360 µmol/L for women and 420 µmol/L for men, according to our lab and French recommendations (Vidal. 2018).

2.5. Histological analysis

One renal biopsy in a 7-years old patient was processed in Department of Pathology, National Health Laboratory Services in University Cape Town (South Africa), using standard techniques for light microscopy and immunofluorescence.

2.6. Statistical analysis

Descriptive data are given as mean ± standard deviation or median and range, if necessary. Student's *T*-test was used for mean comparisons. *P* values < 0.05 were considered as statistically significant.

For comparisons between clinical types, patients were divided in two main groups according to the clinical severity, the first group being composed of type I and III CS and the second group of type II and COFS patients.

3. Results

Among 136 patients with genetically confirmed CS in our cohort, 32 had had renal investigations (23%) and 20 patients out of those 32 (62%) had proteinuria and/or chronic kidney disease (CKD). If we include high blood pressure and hyperuricemia, 22 patients (i.e. 69% of investigated patients) presented with at least one of the targeted disorders (Table 1).

Fifteen out of 21 patients (71% of patients) had hypertension. Mean Blood Pressure (BP) was 121 ± 12 mmHg (+2.11 SDS) and 73 ± 14 mmHg (+1.66 SDS) for SBP and DBP measurement,

Table 1
Tabulation of patients' characteristics: clinical, biological and genetic findings.

	Number of patients (among investigated patients)	Genetic Mutation CSA/CSB	Clinical type COFS/II/I/III
HYPERTENSION	**15/21 (71%)**	8/7	0/5/10/0
Stage 1	5 (24%)		
Stage 2	8 (38%)		
Unknown Stage	2 (9%)		
PROTEINURIA	**10/16 (62%)**	6/4	0/3/7/0
non nephrotic	6 (37.5%)	5/1	0/1/5/0
nephrotic	4 (24.5%)	1/3	0/2/2/0
CKD	**13/29 (45%)**	4/9	1/5/6/1
Stage 2	7 (24%)		
Stage 3	5 (17%)		
Stage 4	1 (4%)		
HYPERURICEMIA	**18/25 (72%)**	9/9	1/4/12/1

respectively. Five patients presented with stage 1 hypertension (24%), 8 with stage 2 (38%) (Table 1). Of these 15 patients, 5 had proteinuria, 3 CKD and 3 had proteinuria and CKD.

No statistically significant difference was found in SBP or DBP between patients with CSA or CSB mutation ($p = 0.62$ and $p = 0.87$, respectively) or clinical type CS I/CS III and CS II/COFS ($p = 0.71$ and $p = 0.56$, respectively).

Proteinuria was found in 10 out of 16 patients (62% of patients who had had a reliable proteinuria measurement). Four patients had nephrotic syndrome (24.5%). All patients with proteinuria had an elevated BP.

GFR was estimated in 13 patients out of 29 (45%), 7 patients presented with stage 2 CKD (24%), 5 with stage 3 (17%) and 1 with stage 4 (4%). Mean GFR was 102 ± 51 mL/min/1.73 m^2. Among these 13 patients, 3 had high blood pressure and 3 had proteinuria and a high blood pressure.

No statistically significant difference was found in GFR between patients with CSA or CSB mutation ($p = 0.05$), although there is a trend towards a lower GFR in CSB patients. A statistically significant difference was found in creatinine GFR between clinical type CS I/CS III and CS II/COFS ($p = 0.04$) (Fig. 1).

Interestingly, nephrotic syndrome and renal failure occurred in the last months or even in the last weeks of life in some of the patients: a 23-year-old boy developed nephrotic syndrome 6 months before his death, a 5-year-old girl developed nephrotic syndrome in the last year of life and a 7-year-old girl showed renal failure and proteinuria without hypoalbuminemia in the last 15 days of life.

Eighteen patients out of 25 (72%) had an increased serum level of uric acid (Fig. 2). The mean serum uric acid value was 423 ± 133 µmol/L. Hyperuricemia was associated with proteinuria in 6 patients, CKD in 8 patients and with high blood pressure in 8 patients.

In our cohort, 2 Cockayne Syndrome siblings had a progressive increase of uricemia over time without renal disease, proteinuria or uricosuria.

No statistically significant difference was found in serum uric acid value between patients with CSA or CSB mutation ($p = 0.72$) or with different clinical subtypes ($p = 0.28$); In our cohort, kidney biopsy was performed in one 7-year-old patient shortly after developing increased BP and nephrotic syndrome. Morphologic features are consistent with membranous glomerulonephritis: glomeruli showed capillary loops with thickening of glomerular basement membrane (Fig. 3A) and non-proliferative glomerular injury and mesangial matrix increase (Fig. 3B). There was no glomerular fibrinoid necrosis or cellular crescent. Abundant granular deposits of IgG and C3 on glomerular basement membrane are seen by immunofluorescence (Fig. 3C and D). Some arteries with fibrinoid necrosis and hyalinization consistent with hypertension were observed. No onion skinning was noted. Tubules and interstitium were preserved.

Eight patients had had a kidney ultrasound. One patient had a very clear asymmetry of the size of the two kidneys and the other a suspicion of nephrocalcinosis. The majority of renal ultrasounds performed in these patients were normal.

4. Discussion

The first descriptions of renal disorders in CS were done five decades ago by Gellis, Ohno and Hirooka, (1966). These last two authors presented 3 patients with proteinuria, 2 out of 3 with hypertension and severe impairment of creatinine clearance.

Others authors have reported renal complications in CS patients but only few patients were involved and the diagnosis of CS was usually not confirmed on a molecular or cellular level in these cases. Nance and

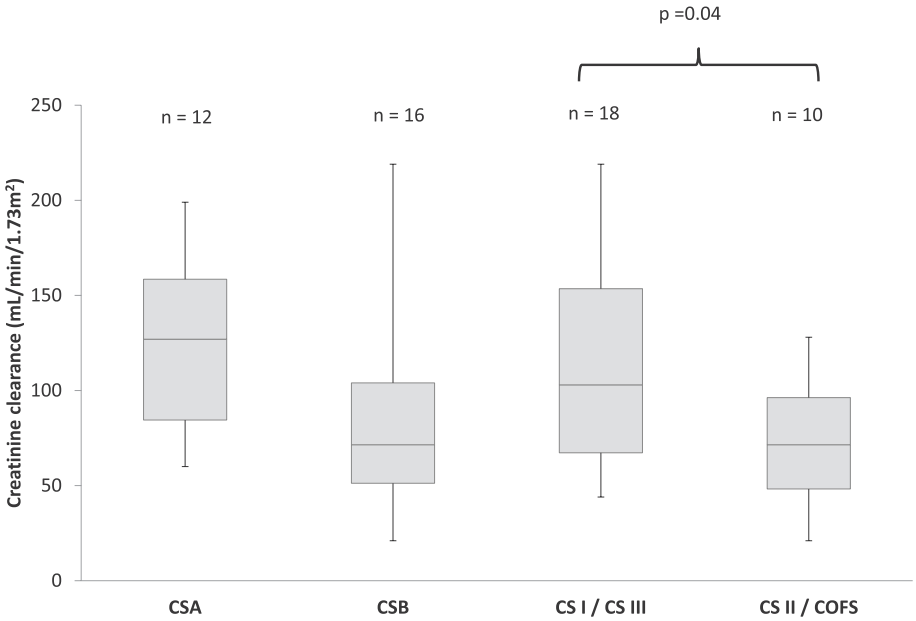

Fig. 1. Creatinine clearance calculated by Schwartz's equation in CS patients according to genetic mutation or clinical type. Each box shows the median value, the inter-quartile range and the minimum and maximum value of creatinine clearance values (Schwartz et al., 2009).

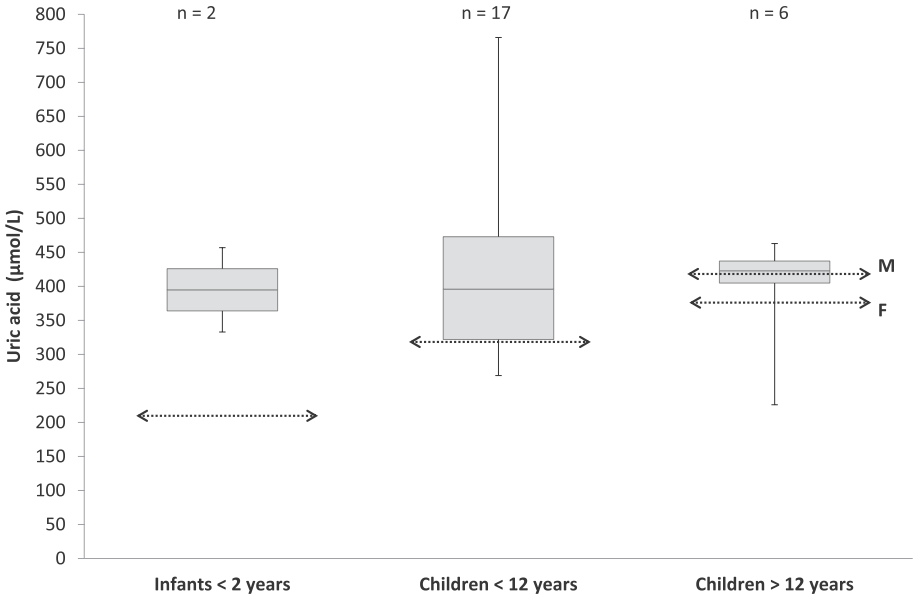

Fig. 2. Serum uric acid value in CS patients grouped according to age. Each box shows the median value, the inter-quartile range and the minimum and maximum value of serum urate value data, the dotted line represents the high norm for age (M = male and F = female).

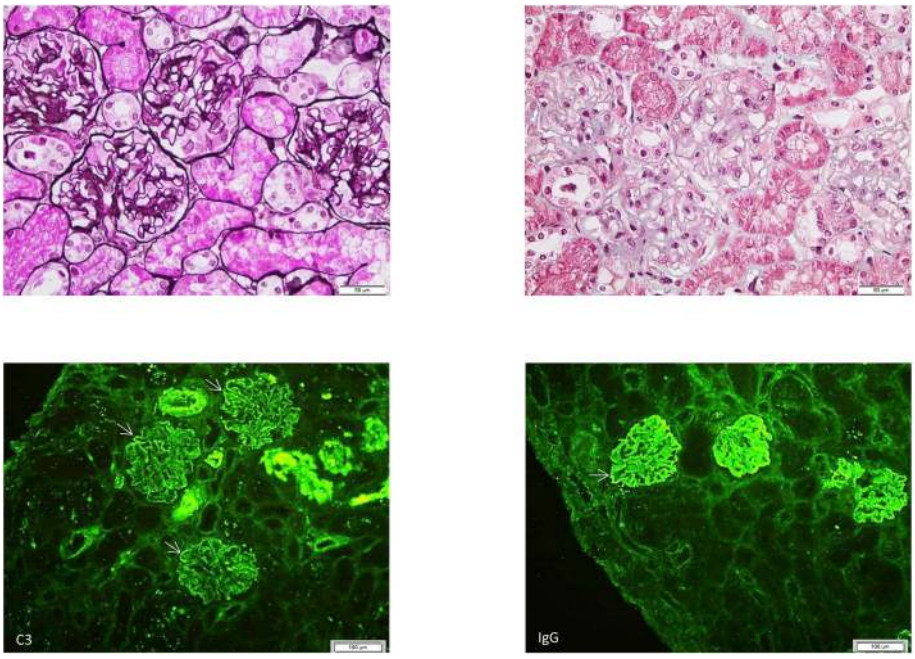

Fig. 3. Histologic findings in the renal biopsy of the patient described in the article. Light microscopy (A) showing morphological features of membranous nephritis with thickening of glomerular capillary loops without increase of mesangial matrix (Silver stain X 200) (B). No proliferative glomerular injury or tubulointerstitial lesions were assessed (Trichrome X 200). Immunofluorescence showing intense granular deposits of C3 (C) and IgG (D) in glomerular membrane (X 100).

Berry described in a review of 140 cases that 10% of patients were developing renal complications including an elevated creatinine and hypertension (Nance and Berry, 1992). More recently Wilson et al. described, in a cohort of 104 patients, hypertension in 18% of patients, a patient with nephrotic syndrome at 6 years, 4 patients presenting with an abnormal ultrasound with an unilateral hypoplastic kidney, an abnormal kidney shape and two patients with renal calculi (Wilson et al., 2016). Kubota et al. in a nationwide survey of CS in Japan found than out of 41 type I CS patients, 10 had renal failure, 11 had proteinuria, and 9 out of 20 patients had high blood pressure. Interestingly, elevated blood urea nitrogen and creatinine were more prominent among the 20 deceased patients. Of the 20 deceased patients, nine had developed severe renal failure during the terminal stage of their condition. Proteinuria was found in 9 out of 11 deceased patients and 2 of 16 surviving patients (Kubota et al., 2015).

In our retrospective study, only 23% of patients have had renal investigations indicating that renal involvement is probably not sufficiently taken into account despite existing reports. Sixty-two percent of those presented with chronic kidney disease and/or proteinuria, confirming a high prevalence of renal impairment. An elevated blood pressure was found in 71% of investigated patients: this prevalence of hypertension is greater than in the few existing studies which have mentioned an incidence of 10–45% of patients with an increased BP or a renal disorder (Kubota et al., 2015; Nance and Berry, 1992; Wilson et al., 2016).

We cannot exclude that this discrepancy might be due to limitations related to BP measurement in our retrospective study: ambulatory BP monitoring or home monitoring was not performed, and some measurements can have been overestimated due to a “white coat hypertension”. Nevertheless, a large number of patients presented with stage 2 hypertension and hypertension was reported to be persistent for most of our patients. Hypertension in CS patient is not necessarily

Table 2
Summary of CS patients with renal disorders and biopsies in review of literature, (BM = Basement membrane; Ig = Immunoglobulin).

Authors	Gender	Age at examination	Clinicobiological renal disorders	Renal biopsy results
Ohno and Hirooka (1966)	M	4 years	Chronic kidney disease, Proteinuria, Hypertension	Thickening of BM and mesangium, collapse or atrophy of capillary loops, hyalinization of glomeruli, atrophy of tubules, interstitial fibrosis. No arteriosclerosis.
Ohno and Hirooka (1966)	M	5 years	Chronic kidney disease, Proteinuria, Hypertension.	Thickening of BM, collapse glomeruli, atrophy of capillary loops, atrophy of tubules, interstitial fibrosis.
Higginbottom et al. (1979)	M	14 years	Hypertension, Proteinuria, Chronic kidney disease	Severe arteriolo- and arteriosclerosis, mild increase in mesangial matrix. Cellularity, glomerular BM and tubules are normal, no interstitial fibrosis. Normally thickening glomerular BM, collapsed peripheral capillary loops, focal segmental irregular deposits of IgG, M and C3 within glomeruli
Higginbottom et al. (1979)	F	3 years	Hypertension, Chronic kidney disease	Granular deposits in the subendothelial region of glomerular BM, increase in mesangial matrix and cells, splitting of BM, segmental granular deposits of IgG, M and C3 in glomerular BM and mesangium.
Sato et al. (1988)	M	9 years	Proteinuria, Chronic kidney disease	Global sclerosis of glomeruli, thickening of the capillary walls and expansion of the mesangial matrix, no significant deposition of Ig or complement, homogeneous thickening of the glomerular BM
Hirooka et al. (1988)	F	5 years	Proteinuria, Hypertension	Paucity of capillary loops, thickening capillary walls, some glomeruli with advanced lesions showed collapse of the glomerular tufts or complete hyalinization, atrophy of tubules and interstitial fibrosis. No arteriosclerosis. Thickened glomerular BM.
Nance and Berry (1992)	10% CS patients with renal complications: hypertension, decreased creatinine clearance, proteinuria			Thickening BM of the glomeruli, mesangium and tubules, interstitial fibrosis, tubular atrophy, hyalinization of glomeruli, thickening or atrophy of capillary loops
Reiss et al. (1996)	M	5 years	Nephrotic syndrome, acute hypertensive crisis with hemiparesis	Focal segmental glomerulosclerosis
Funaki et al. (2006)	F	12 years	Chronic kidney disease, Hyperuricemia, hypertension, Nephrotic syndrome	Acute tubulointerstitial nephritis: glomeruli globally sclerotic, insufficient format of capillary loops, atrophy tubules, young fibrosis with oedema and cell infiltrate, inflammatory cells in tubules. No deposits of Ig or complement. Hyaline arteriosclerosis. Thickening of glomerular BM and increment of mesangial matrix with capillary collapse.
Forsythe et al. (2009)	1 child	7 years	nephrotic syndrome	Glomerular sclerosis, tubular atrophy, interstitial fibrosis and hyaline thickening of the arteriolar wall.
Kubota et al. (2015)	F	8 years	Chronic kidney disease stage 5, Hypertension	Global glomerulosclerosis, a tortuous and thickened BM, disappearance of podocytes and renal tubular narrowing without mesangial proliferation.
Ben Chehida et al. (2017)	F	13 years	Nephrotic syndrome, moderate kidney failure	Cystic focal segmental glomerulosclerosis with collapse in glomeruli, glomerular BM normal, few arterioles with hyaline arteriosclerosis especially around the glomerulus, interstitial fibrosis, atrophic and dilated tubules, no cell proliferation. Large deposits of IgM along the capillary walls, with segmental lesions and complement C3 along arteriolar walls.
Delfils et al. (2019)	M	7 years	Nephrotic syndrome, hypertension	Membranous glomerulonephritis: glomeruli showed capillary loops with thickening of glomerular BM and non-proliferative glomerular injury and mesangial matrix increase. Abundant granular deposits of IgG and C3 on glomerular basement membrane are seen by immunofluorescence. Some arteries with fibrinoid necrosis and hyalinization consistent with hypertension were observed.

related to a renal disorder but can be related to arteriosclerosis with an accelerated ageing process (Rapin et al., 2006). In our cohort, only 6 patients had both high BP and CKD and 10 patients had BP and proteinuria, but 2 were hypertensive without renal disease. Hypertension is a powerful predictor of morbidity and mortality in the general population and probably plays a role as a factor of acceleration of decline in GFR in CS patients (National High Blood Pressure Education Program Working Group on High Blood Pressure in and Adolescents, 2004; National Kidney, 2002). Hypertension is probably underdiagnosed in CS patients, because the threshold for hypertension is lower than those of the children of the same age because their height is systematically lower than the 5th percentile (National High Blood Pressure Education Program Working Group on High Blood Pressure in and Adolescents, 2004). One other pitfall in the BP assessment in CS children is the use of chronological age for BP estimate, knowing that CS patients have features of premature aging. Aging process cannot be properly quantified and we therefore used chronological age, but we are aware that it can have led to an overestimate of hypertension. Abnormal nutrition in CS patients could also impact BP, malnutrition has been associated with increased blood pressure in childhood (Sesso et al., 2004; Sawaya et al., 2005). However the metabolism of CS patients is presently unknown and preclinical studies are under way.

We believe that BP measurement should be frequently assessed in CS patients and that left ventricular hypertrophy monitoring is required in these patients.

Renal failure exists in 45% of investigated CS patients in our study, compared to 29% in the Japanese cohort (Kubota et al., 2015). Because of the decreased muscle mass in CS, creatinine probably under-estimates CKD in these patients. Motojiba and al showed in 2014 that serum creatinine corrected for height is useful for evaluating renal function in CS patients (Motojima et al., 2014). These children are usually not dialyzed or transplanted because their renal disorders are associated with an incurable multi-system disorder resulting in a very poor quality of life and a reduced lifespan. This retrospective study did not collect data on cystatin C levels, but this measure could be valuable to better determine renal function.

Proteinuria was highly prevalent in our cohort (62% of investigated patients) and 24.5% of investigated patients had nephrotic syndrome. 5 cases of nephrotic syndrome and 15 cases of mild proteinuria have been previously reported and proteinuria was highly prevalent in CS patients in the Japanese cohort (Funaki et al., 2006; Kubota et al., 2015; Reiss et al., 1996; Sato et al., 1988; Wilson et al., 2016). Proteinuria leads to a worsening of renal function. We believe that proteinuria monitoring is mandatory. In this regard, ACE inhibitors may help slow down the progression of renal disease in CS patients.

In our study, hyperuricemia was found in 72% of investigated patients. Hyperuricemia was previously reported in a case report. Uric acid is mostly cleared by the kidney, and its level rises with declined GFR (Funaki et al., 2006). Hyperuricemia can be secondary to increased production or to decreased elimination secondary to the kidney failure. Hyperuricemia is an independent risk factor for faster progression of CKD in patients (Feig, 2009). Some studies have shown a positive relationship between uric acid and BP (Alper et al., 2005; Goldstein and Manowitz, 1993). Uric acid is increased in CKD but is also associated with CKD progression (Fathallah-Shaykh and Cramer, 2014).

We were able to show that elevated uric acid was present before renal failure in two siblings, and therefore we believe that hyperuricemia can be considered as an independent factor in CS patients. However, GFR decline can have been underestimated by creatinine in these patients and a better renal function estimate should be performed in these patients to confirm our hypothesis. An anti-uric acid medication can be discussed in CS patients.

Only two patients had abnormalities on renal ultrasound. No major congenital structural abnormalities were found in previous studies (Nance and Berry, 1992; Wilson et al., 2016).

No correlation between CS genetic background (*CSA* or *CSB* mutations) or clinical subtype and kidney disease could be found, except for a correlation between severe renal insufficiency and more severe phenotypes: COFS and CS II. However these results need to be confirmed in a larger number of patients.

Only a small number of kidneys biopsies have been performed in CS patients (Table 2). In our study, one renal biopsy was done in a child with CKD, high blood pressure and nephrotic syndrome and showed a membranous glomerulonephritis, with evidence of malignant hypertension. To our knowledge it is the first case of CS patients reported with membranous glomerulonephritis. Most of the biopsies in the literature were showing nephron reduction lesions and arteriolosclerosis and some authors reported tubulointerstitial lesions (Funaki et al., 2006). Glomerular basal membranes were sometimes thickened without deposit by immunofluorescence. Deposits of IgG and C3 were previously reported, but associated with focal segmental glomerulosclerosis, which was not the case in our patient.

The exact mechanism of renal impairment in CS patients remains elusive, and only limited clinical data and histological findings are available. Still, we can hypothesise that some renal lesions are likely related to an accelerated ageing process. Most biopsies showed signs of vascular involvement, with arteriolosclerosis or glomerular hyalinosis, which could be the mechanism, causing renal disorder and hypertension may play a major role (Higginbottom et al., 1979; Hirooka et al., 1988; Nance and Berry, 1992; Ohno and Hirooka, 1966; Rapin et al., 2006; Ben Chehida et al., 2017). These abnormalities have been reported, on the vessels of other organs in these patients, especially on the vessels of brain (Wilson et al., 2016). A follow-up by measurement of the resistance indices by renal Doppler echography could be of interest. More interestingly, in the group of nucleotide excision repair disorders, xeroderma pigmentosum patients were also reported with an increased risk of renal impairment but this was not reported in trichothiodystrophy patients (Faghri et al., 2008; Kondo et al., 2016; Trabulus et al., 2012). Recently, it has been suggested that mitochondrial dysfunction could play a role in CS patients, but it remains controversial. Features in CS patients are not fully explained by nucleotide excision repair disorder and it was speculated that CS proteins have an addition role (van Gool et al., 1997). CSA and CSB have been detected in the nucleus and mitochondria and altered mitochondrial transcription has been identified in immortalized CS cells. CSB has been found to affect mitochondrial turnover and function and overexpression of a mitochondrial serine proteinase was found in CS cells in a recent study (Chatre et al., 2015). Mitochondrial deficiencies are frequently associated with renal impairment and nephrotic syndrome, but it is unclear if this mechanism could explain part of the renal impairment in CS (Scheibye-Knudsen et al., 2013).

CS patients and Schimke immune-osseous dysplasia (SIOD) patients share some clinical similarities. SIOD is an autosomal recessive disorder characterized by the combination of a progressive proteinuric glomerulopathy with spondyloepiphyseal dysplasia, growth retardation, intellectual delay, defective cellular immunity, hair and teeth abnormalities and abnormal skin pigmentation (Morimoto et al., 1993). This disease is caused by biallelic mutations in the *SMARCAL1* gene, which impair DNA double strand break repair. Renal failure occurs before the age of 12 years in 64% of SIOD cases. A constant proteinuria with nephrotic syndrome is described and histological findings are focal and segmental glomerulosclerosis, mesangial proliferation or tubulointerstitial lesions (Boerkoel et al., 2000). Similar histological lesions were described in Cockayne Syndrome patients. These two syndromes due to a DNA repair impairment have common clinical features: short stature, mental retardation and skin abnormalities. Moreover CSB and SMARCAL1 protein belong to the same SNF2 family of proteins and exhibit 32% of analogy with NCBI BLAST (Basic Local Alignment Search Tool). Lipska and al. recently suggested looking for *SMARCAL1* mutations in patients with corticoresistant nephrotic syndrome and short size (Lipska-Zietkiewicz et al., 2017). We similarly suggest looking at *CSA* and *CSB* mutations in patients with corticoresistant

nephrotic syndrome associated with photosensitivity or growth retardation.

In conclusion, our study demonstrates that renal disease is frequent and potentially life-threatening in CS patients and that it remains largely underinvestigated and we would like to raise clinician's awareness of this issue.

We believe that a nephrological follow-up is required in CS, and that CS patients may benefit from adequate treatment for hypertension and hyperuricemia.

Conflicts of interest

The authors have nothing to declare.

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