Pediatric urogenital schistosomiasis diagnosed in France

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Research Article

Keywords: Schistosomiasis, Schistosoma haematobium, urogenital, pediatric, migrant

Posted Date: July 13th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3149370/v1

Version of Record: A version of this preprint was published at Pediatric Nephrology on January 12th, 2024. See the published version at https://doi.org/10.1007/s00467-023-06260-x.

Abstract

Introduction:

Schistosomiasis affects approximately 230 million people worldwide. With the rise of international travel and immigration from endemic areas, there is an increase incidence of imported urinary schistosomiasis cases in France witch raise the risk of indigenous cases as observed in Corsica. European pediatricians are not used to this pathology. The objective of this study is to provide a better description of the clinical and paraclinical characteristics and the evolution of affected children.

Material and methods:

We contacted all French pediatric centers that may have treated children with urinary schistosomiasis, between 2013 and 2019, through the French pediatric nephrology society and the pediatric infectious pathology group. Age, sex, comorbidities, initial and follow-up clinical, biological and radiological characteristics were collected retrospectively.

Results:

A total of 122 patients from 10 different centers were included. The median age was 14 years and the sex ratio M/F was 4:1. Hematuria was present in 82% of the patients while urinary tract abnormality were found in 36% of them. 14 patients (11%) presented with complicated form of urinary schistosomiasis including 10 patients with renal failure. All patients received treatment with praziquantel, which was well tolerated and led to clinical resolution of the disease in 98% of cases.

Conclusion:

The diagnosis, management and follow-up of genital schistosomiasis must be improved, particularly by implementing systematic screening of patients returning from endemic areas, conducting renal ultrasounds and searching for nephrological complications such as renal failure and persistent proteinuria. A prospective study to evaluate long-term complications is essential.

Introduction

Schistosomiasis, a neglected disease according to the WHO (1), is a parasitic disease caused by 6 species from Schistosoma genus. The most prevalent species are *Schistosoma haematobium* (Sh) and *Schistosoma mansoni (Sm)*. Ranking second in morbidity and mortality after malaria, it affects between 200 and 400 million people worldwide (2). Urogenital schistosomiasis (US), due to Sh, is endemic in intertropical Africa and Madagascar and particularly affects young adolescents (3, 4). In endemic regions, the initial infection usually occurs before the age of 2, and symptoms worsen during the first decade of life (5). The diagnosis is sometimes complex due to the heterogeneity of clinical and biological presentations. Often schistosomiasis remains asymptomatic, especially in children (6). In high-

prevalence areas, hematuria is commonly misinterpreted as a natural sign of puberty or menstruation in girls and therefore be considered asymptomatic for the patient (7).

While the incidence of autochthonous schistosomiasis in non-endemic areas is decreasing (8), it remains one of the most frequently imported diseases among children returning from endemic area (9, 10). With increased international travel and immigration from endemic areas, the incidence of imported cases of schistosomiasis in France is on a rise, thereby elevating the risk of indigenous cases as observed in Corsica (11). However, there are few studies describing cohorts of imported cases of schistosomiasis (6, 9, 12)

Currently, there is no definitive diagnostic test for schistosomiasis. Since January 2017, the French health society (HAS) recommended screening all individuals returning from endemic areas for this parasitosis, regardless of symptoms (13). The present recommendations rely on a combination of serological tests and parasitological examination under a microscope. Confirmation of serology by Western blot (WB) currently appears to be one of the most effective technique (14). Hypereosinophilia provides diagnostic guidance, especially in the acute phase, although it is not always present (15). Urine dipstick tests for microscopic hematuria or leukocyturia provides guidance but are insufficient for a conclusive diagnosis.

Praziquantel is the recommended treatment for urinary schistosomiasis (16). It is a safe, cost-effective, and efficient treatment option. In endemic areas, the schistosomiasis control strategy involves repeated treatment without ultrasound, serological or parasitological control. In European countries, where schistosomiasis is one of the most common neglected tropical disease (17), it mainly affects migrant populations whith limited access to healthcare systems.

The aim of our study was to analyze imported pediatric urinary schistosomiasis in children in France, in order to provide a clinical, biological and radiological overview of this infection in migrants and travelers

Material and Methods

We contacted participating centers through the French Pediatric Nephrology Society and the French Pediatric Infectious Pathology Group. Once a center agreed to participate, the referring clinician collaborated with local parasitology laboratory and the infectious diseases department to ensure completeness of the patient files in each center. We retrospectively included pediatric patients diagnosed with urinary schistosomiasis in France.

The diagnosis of US was based on urine parasitological examination (UPE) with or without PCR, ELISA and Western Blot serology and/or anatomopathology findings. The techniques used for serology or PCR varied across institutions, and it was not always possible to extract this information for every patient. During data collection, we were unable to define whether EPU had been associated in conjunction with PCR. The invasive phase was defined by the presence of fever, myalgia, headache, asthenia and hypereosinophilia associated with positive serology.

Patient data including age, sex, comorbidity, country of birth and infection, biological, imaging or consultation reports, were anonymized and analyzed using a secured computer system. Renal failure was defined as an eGFR < 35ml/min/1,73m² according to the pRIFLE classification (18).

Data analysis was performed using means and medians. Statistical analyses were performed using R® software Version 3.1.3 (09.03.2015). A Mann-Whitney test was used for quantitative data. Some of the patient data analyzed in our study had been previously published (13).

This study recceived approuval from the ethics committee of the Centre Hospitalier du Val d'Ariège, the study sponsor and the study information was submitted to “La Commission Nationale de l'Informatique et des Libertés” (CNIL).

Results

A total of 122 patients from ten French University hospitals were included in the study (Fig. 1). These patients had been diagnosed with Sh infection in France from 2013 to 2019. Diagnosis was made by various healthcare providers: health care access service for 26 patients (21%), pediatrician for 25 patients (20%), adult nephrologist for 20 patients (16%), emergency physician for 16 patients (13%), infectiologists for 11 patients (9%), general practitioner for 10 patients (8%), other practitioners for 14 patients (11%).

Clinical characteristics:

Twenty-seven children (22%) were infected during travel, including 26 children born in France. The remaining 95 children (88%) were migrants, who arrived in France on average 6 months (1–60) prior to diagnosis. Their countries of origin are detailed in Table 1.

Table 1
Population characteristics

		Population (n = 122)
Clinical data	Age on diagnosis (year), median	14 (3–17)
	Age on symptoms (year),	11 (3–16)
	Sex ratio M/F	4.1
	Weight (kg), median	49 (14–88)
	Height (cm), median	156.6 (101–189)
	Migrant, n (%)	95 (78)
	Unaccompanied minor, n (%)	54 (49)
Country of origin	France, n (%)	27 (22)
	Guinea, n (%)	10 (8)
	Ivory coast, n (%)	16 (13)
	Mali, n (%)	47 (39)
	Mauritania, n (%)	6 (5)
	Senegal, n (%)	6 (5)
	Tchad, n (%)	3 (2)
	Others, n (%)	6 (5)
Country of contamination	France (Corsica), n (%)	8 (7)
	Guinea, n (%)	10 (8)
	Ivory coast, n (%)	16 (13)
	Mali, n (%)	63 (52)
	Mauritania, n (%)	6 (5)
	Senegal, n (%)	8 (7)
	Tchad, n (%)	4 (3)
	Others, n (%)	7 (6)

		Population (n = 122)
Symptoms	State phase, n (%)	108 (99)
	Hematuria, n (%)	96 (82)
	Proteinuria	14 (19)
	Urinary dysfonction, n (%)	15 (12)
	Lower back pain, n (%)	13 (11)
	No symptoms, n (%)	2 (3)
	Symptom onset time (month), median	12 (0–72) (n = 105)
	Time to diagnosis (month), median	6 (1–48) (n = 56)

Among the 122 patients, 19 (15.6%) had SU diagnosis before the onset of symptoms. The median age was 14 years and the male-to-female ratio M/F was 4:1. Only one patient had invasive schistosomiasis at inclusion. Initially, hematuria was present in 100 patients (82%) while proteinuria was present in 24 patients (20%). A total of 14 patients (11%) had complicated disease: 2 epididymitis, 1 bladder stenosis, 1 ureteral stenosis and 10 renal failures

Among patients born in France, 2 (8%) had another infectious disease. Among migrant patients, 40 (42%) had another ongoing or cured infectious disease (9 Amoebiasis, 8 malaria, 7 hepatitis B, 2 hepatitis C, 5 tuberculosis, 5 strongyloidiasis, 2 tapeworms infection, 1 filariasis and 1 granulomatous lymphangitis) (p = 0.05)

Biological characteristics:

UPE was performed in 110 patients with 96 positive samples (87%). Stool parasitology was performed in 46 patients with 25 positive samples (54%). Several data regarding serology were missing, preventing differentiation of ELISA and Western Blot sensitivities. Serologies (ELISA and WB combined) were performed for 86 patients with 75 positive samples (87%). (Fig. 3) Schistosoma serology was controlled in last check-up 22 times and remained positive in 13 patients with decreased antibodies levels.

Eosinophilia was found in 93 patients (72%). At follow-up, eosinophils were controlled in 32 cases, showing increased level in 12 patients and normalized levels in 13 patients.

Increase total IgE was observed in 9 patients (50%) and remained elevated at last check-up for 5 patients. Proteinuria was observed in 14 patients (19%) and decreased glomerular filtration rate in 9 patients (17%). Hematuria was observed in 96 patients (82%) and proteinuria in 14 patients (19%).

Imaging characteristics:

Ultrasound of the urinary tract was performed in 96 patients. Abnormality was detected in 44 patients (36%), which mainly consisted of classic elements such as urinary bladder wall polyps, bladder sediment,

bladder thickening or calcification. More severe abnormality were present in 7 patients (12%) including renal pelvis dilatation, epididymitis, renal parenchyma involvement (Fig. 3). In retrospect, we evaluated the abnormal ultrasounds using the Niamey score (27). Main score obtained was 3.1 (1–14). Two patients had normal ultrasound before and after treatment. Nineteen patients had normal ultrasound after treatment, while 16 patients had persistent ultrasound abnormalities with a main Niamey score of 2.6. The timing of ultrasound follow-up varied from one to 6 months.

Five patients underwent cystoscopy to explore a bladder mass. Two patients underwent urinary flow measurement, one of whom was pathological results.

Treatment:

Eighty-six patients (77%) received a single dose of praziquantel 40mg/kg. Four patients (4%) received a dose of 50mg/kg in two days. For 11 patients (9%) lost to follow-up, we lacked data on the praziquantel dosage and administration. For 20 patients (16%), a second dose of praziquantel was given. The reason was a complicated form for 2 patients (bladder stenosis and pyloric dilatation), a co-infection with *Schistosoma mansoni* for 2 patients, a treatment failure with positive UPR for 2 patients, the persistence of a positive serology for one patient. We did not have treatment information on the remaining 11 patients. 1 patient did not received praziquantel

The treatment tolerance was good, 3 patients presented adverse effects (2 vomiting and one pruritus). One patient underwent surgery for bladder dilatation. During the last follow-up, persistent hematuria was observed in 9 patients and proteinuria in 3 patients.

Follow-up:

Seventy-one patients (58%) had a follow-up visit from 1 to 12 month after treatment. Among them, 35 patients (49%) underwent ultrasound, with 16 still showing abnormalities, 13 normalized and 6 remaining normal (Fig. 2). UPE was perform in 45 patients (63%) including 7 patients with persistent *Sh* infection, urinary sample for proteinuria or hematuria was perform in 46 patients (65%). 8 patients (17,5%) had persistent hematuria and 3 patients (6,5%) persistent proteinuria. blood sample (serology, eosinophilia) were perform in 44 patients (62%) with 22 patients (50%) showing persistent eosinophilia.

Discussion

Hs infection is a common diseases among children returning from tropical regions (10). However, this pathology is poorly known by pediatricians in non-endemic areas and patients (19). In our study, the average delay between arrival in France and diagnosis often exceeded 6 months. In our study, only 19 patients had received treatment before the onset of clinical signs. Similar delays in diagnosis have been observed in US (3, 20). To address this issue, the French health authority has recommended systematic screening for schistosomiasis in individuals returning from endemic areas since 2017 (13, 21). Screening of migrant patients is mainly carried out by health care access services or by general practitioners (22) while hospitals are more likely used to symptomatic patients. Our retrospective collection of data in

university hospitals may introduce bias, as the study population may over-represent the most severe cases and those less involved in conventional follow-up. Asymptomatic patients were few, making the study population less representative of the general population (23).

The majority of patients included were migrant children. We can hypothesize that French travelers to schistosomiasis-endemic areas were better informed about the risks of Hs contamination through traveler's consultations, and had shorter periods of exposure (34, 35).Additionally, we found a higher prevalence of bacterial or parasitic coinfections among migrants patients (15). Four patients in our cohort were infected during the Corsican US epidemic. They did not present any complications.

The median age at diagnosis was 14 years and the male-female sex ratio was 4.1. These findings are consistent with studies conducted in Western countries (24). However, the sex ratio found in epidemiological studies in endemic areas is close to 1.1 (25, 26). The predominance of infected boys in our study can be partly attributed to the fact that the majority of included children were unaccompanied minors (65%) who are predominantly male (22). Other factors such as underreporting of urinary symptoms in girls or limited acces to healthcare for woman may also contribute to this gender imbalance (27).

Five patients in our cohort had complicated forms: two epididymitis, one bladder stenosis, one ureteral stenosis and one renal failure. Creatinine measurement was absent in 50% of the files and ultrasound was absent in 12 patients (17%). An ultrasound anomaly was present in 55% of cases. However, the search for complication by ultrasound is essential to monitor the post-treatment evolution. In an adult cohort of 241 patients, Abdou *et al* reported 7 cases of bladder dilatation, 12 of ureteral dilatation and 15 of bladder cancer (28). In another study by Hodel *et al*, the presence of Hs infection was associated with an increased risk of chronic renal failure (OR 2.5)(29). Finally, a Barcelona study on imported schistosomiasis found even 30% renal failure in their adult patients (30). Given the major long-term complications, it seems essential to screen patients who have visited an endemic area and to organize screening, treatment, biological and ultrasound follow-up (31) as well as screening of infertility outcome (32, 33). Only 20% of patients had schistosomiasis diagnosis from a pediatrician and the median delay to diagnosis was of 6 month. These two data show the lack of knowledge of this pathology in pediatrics and underline the necessity of a better training on this pathology. Indeed, the earlier patients are treated for their schistosomiasis, the fewer complications they will have (34).

The biological diagnosis of US is complex. We found hypereosinophilia in 71% of cases, more than usually found in epidemiological studies (50% of hypereosinophilia found in Italy) (24). The combined ELISA and WB serologies were positive in 77% of patients. Stool parasitology had a low cost-effectiveness but seems essential to detect parasitic co-infections in migrant patients. UPE combine with PCR was the most sensitive test, positive in 93% of patients. These data are consistent with those reported in the literature (35).

We observe a lack of biological control of healing in follow-up. EPU control was searched in 15 patients (12,3%). This may be due to a high rate of lost-to-follow-up as well and a reluctance of asymptomatic

patients to undergo futher tests.. A serological control was performed in 28 patients (14,8%) with a decrease in antibody titer, as expected. The urinary eosinophil cationic protein test (36) was performed in only one patient, so its effectiveness in the follow-up remains inconclusive.

A total of 109 patients received praziquantel with two case requiting a second dose due to treatment failure. Treatment failure has been reported in the literature (37, 38), underscoring the importance of parasitological follow-up in imported schistosomiasis cases. Adverse effets of praziquantel treatment were reported in 3 patients (2 vomiting and one pruritus). This rate is low in our cohort (39), probably due to an information bias. Many patients didn't have detailed follow-up consultation reports and simple adverse events such as abdominal pain were probably underestimated. Unfortunately, information on previous preventive treatment with praziquantel in patients' country of origin was not available. Giving the high rate of lost to follow-up and the low rate of adverse event of praziquantel treatment, its systematic use for the migrant population could be an effective approach (6). However, this choice should not overshadow the need for effective screening of complications and a long-term follow-up (40)

Conclusion

This multicenter study provides valuable insights into imported pediatric US, including the high prevalence of kidney disease in this population. With increased immigration from Africa and the presence of mollusks in southern Europe, it is crucial to improve screening and management of schistosomiasis in travelers and migrants. The objective is twofold: to prevent complicated forms of the disease and to limit the risk of autochthonous outbreaks. Management of infected patients should include biological and imaging examinations to assess renal or genital involvement. Enhancing medical knowledge of this pathology among all practitioners is essential to improve care and outcomes.

Declarations

Conflict of Interest: The authors declare that they have no conflicts of interest

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Figures

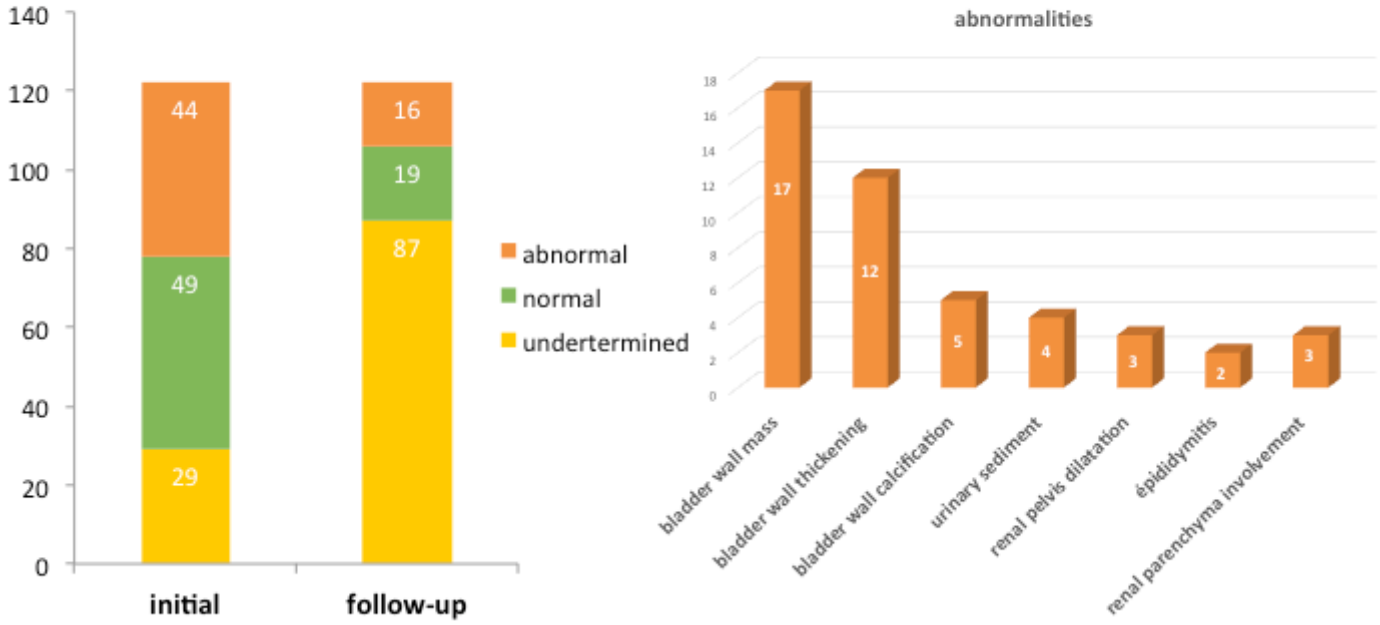

Figure 1

study centers and number of patients included

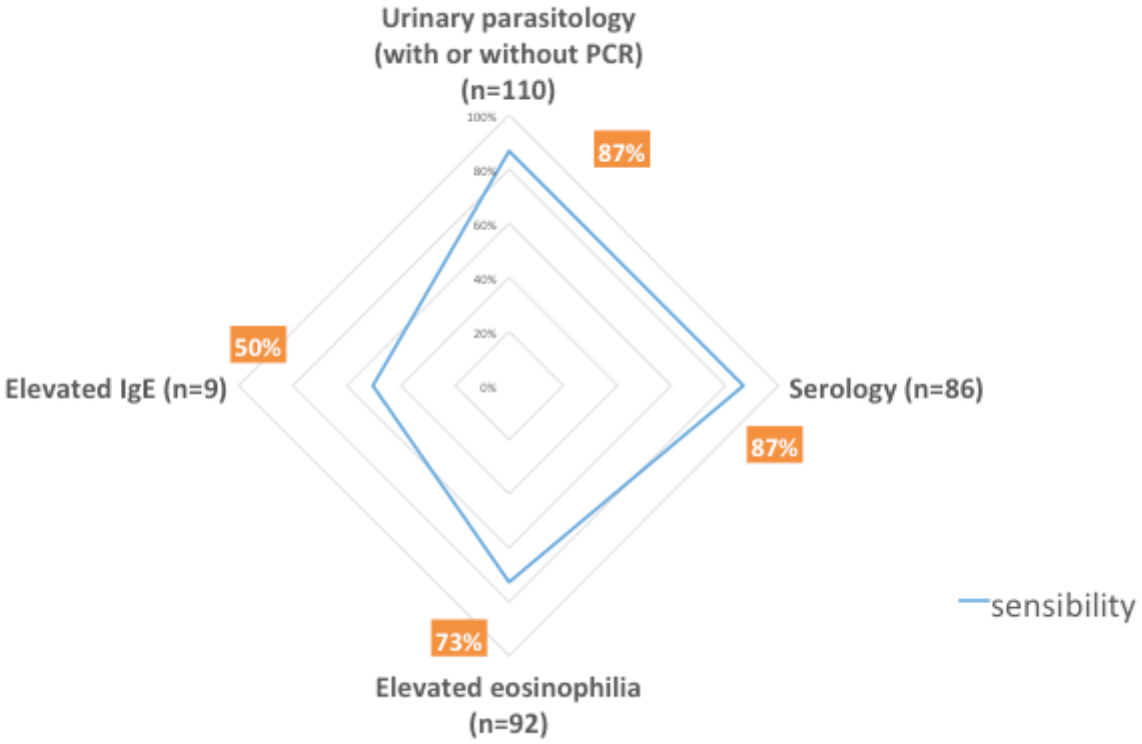

Figure 2

sensitivity of biological tests in percentage, n corresponding to the number of tests performed in our cohort

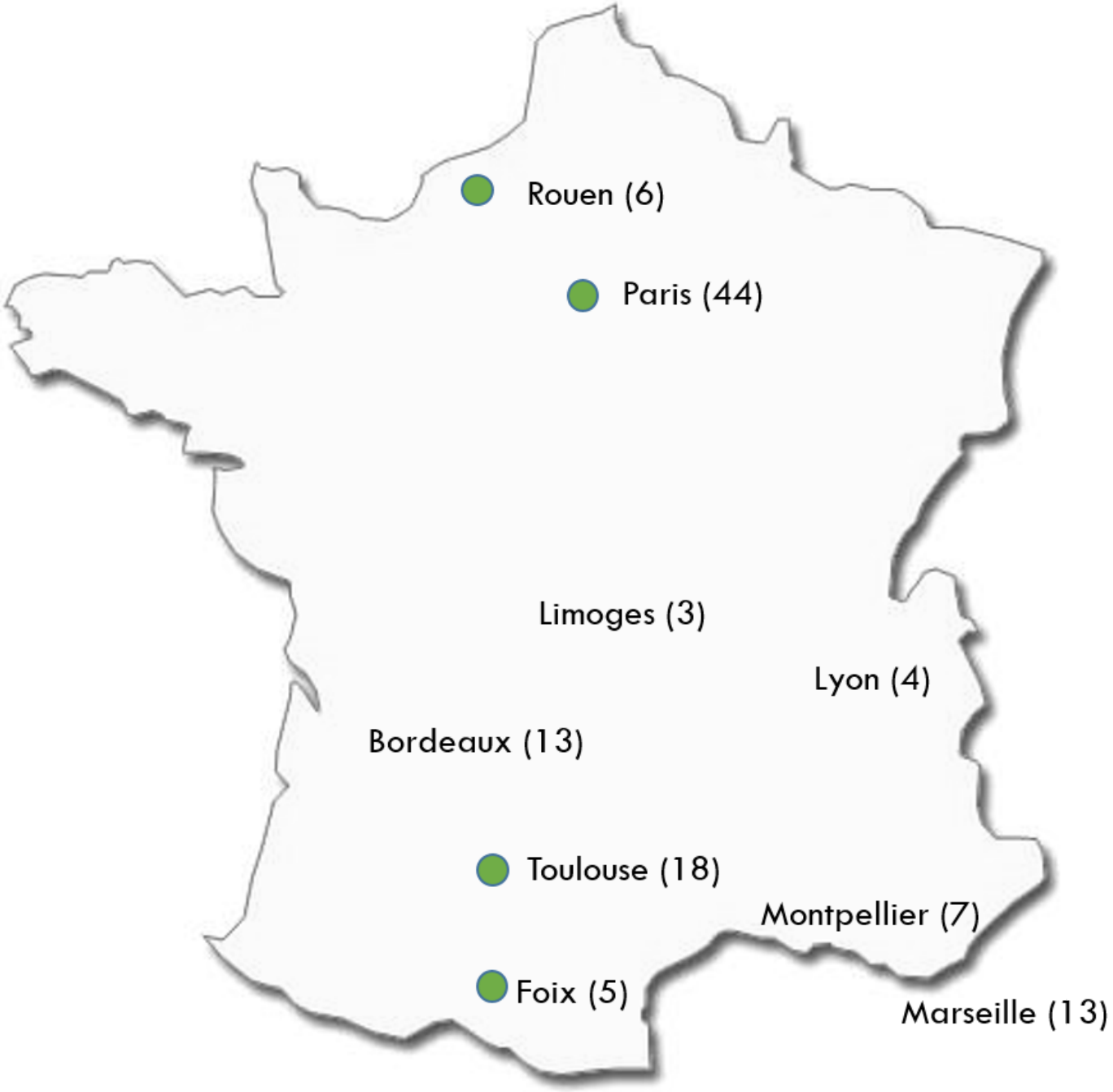

Figure 3

Ultrasound renal abnormalities at diagnosis and follow up and detail of abnormalities found at diagnosis