CHRONIC KIDNEY DISEASE AND AN UNCERTAIN DIAGNOSIS OF FABRY DISEASE: approach to a correct diagnosis

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Introduction

- Screening for Fabry disease (FD) among kidney disease patients reveals a large number of individuals with a variant in the α-galactosidase A (GLA) gene, who are lacking Fabry characteristics
  table 1 for diagnostic criteria
- These individuals may have non-classical (NC) FD or no FD at all.
- The impact of a wrong diagnosis is huge, as it causes anxiety for families, inappropriate counseling and initiation of extremely expensive and burdensome enzyme therapy
- A structured diagnostic approach is warranted

AIM:

To develop a **diagnostic algorithm** on how to approach an individual with chronic kidney disease and an **uncertain diagnosis of FD nephropathy**.

Table 1. diagnostic criteria

Definite diagnosis of FD
GLA variant *and* ≤5% GLA activity (leucocytes, mean of reference value, males only) *with either* ≥1 characteristic FD sign: neuropathic pain, cornea verticillata, clustered angiokeratoma *or* plasma (lyso)Gb3 in the range of classical males *or* a family member with definite FD
Uncertain diagnosis of FD
Subjects with a GLA mutation and a non specific signs, such as LVH or proteinuria, failing definite criteria

Methods

A systematic review was performed to identify imaging and laboratory criteria that could confirm or exclude FD

A modified Delphi procedure with 3 rounds was conducted among 11 FD experts

Criteria were accepted in the algorithm if there was ≥75% agreement and no disagreement

Table 2. Rejected diagnostic criteria

To confirm FD	To exclude FD
Renal cysts	Absent renal cysts
Immunohistochemical staining of Gb3 in urine	Small kidneys
Maltese cross sign in urine	High proteinuria
High urinary Gb3 (classical male range)	

Results

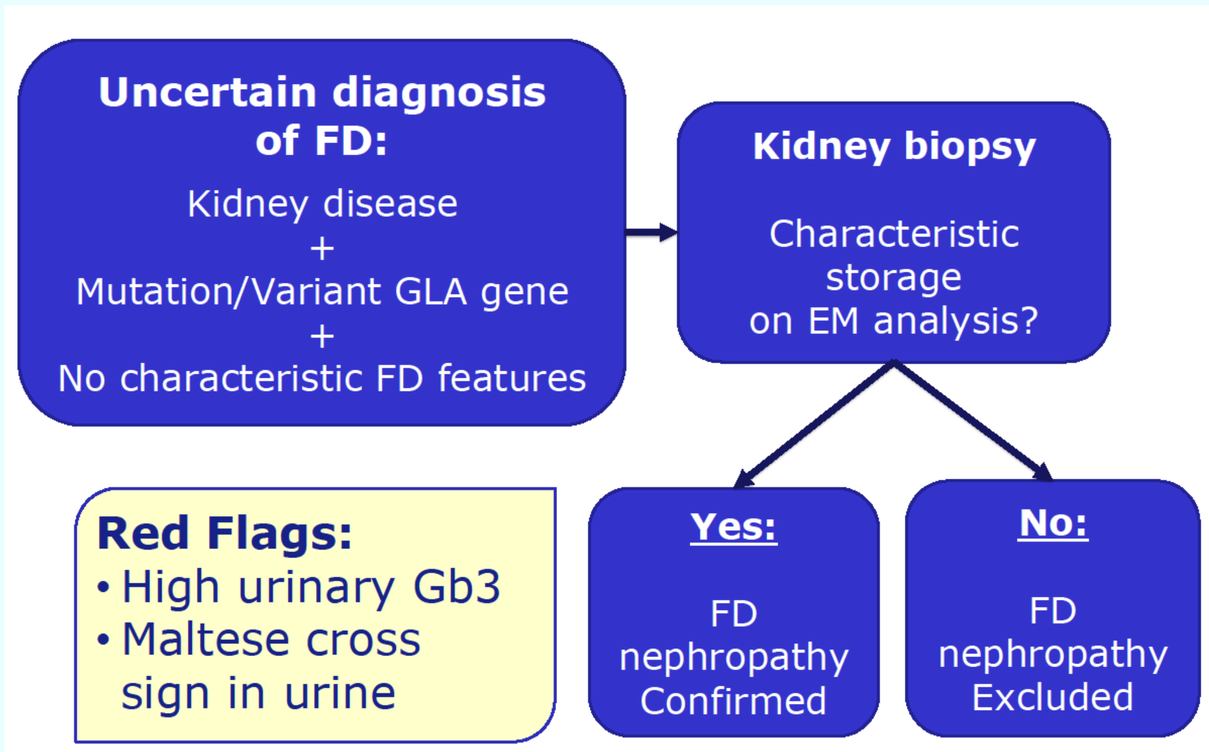

Figure 1. Diagnostic algorithm

Figure 1, Table 2

- The current gold standard was defined as characteristic storage on electron microscopy (EM) in a kidney biopsy, in the absence of medication use that may induce similar storage
- Most criteria were rejected by the experts because of low or uncertain specificity
- Recent data suggest that urinary Gb3 may also be increased in other diseases, thus its specificity was debated
- There was no agreement that urine Gb3 can confirm a diagnosis of FD, although one-third of the panelists indicated that high urine Gb3 is sufficient to confirm FD
- High urinary Gb3 and Maltese cross sign in urine were selected as 'red flags', indicating that FD is more likely, but a biopsy is still needed to confirm or reject the diagnosis

Conclusion

In adults with kidney disease, a GLA variant and an uncertain diagnosis of FD:

- **A kidney biopsy with EM analysis** should be performed to confirm or reject the diagnosis of FD nephropathy
- Other criteria currently cannot substitute for a biopsy in these cases

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