

# Females with Fabry disease

compared to males where are the differences  
and are they important?

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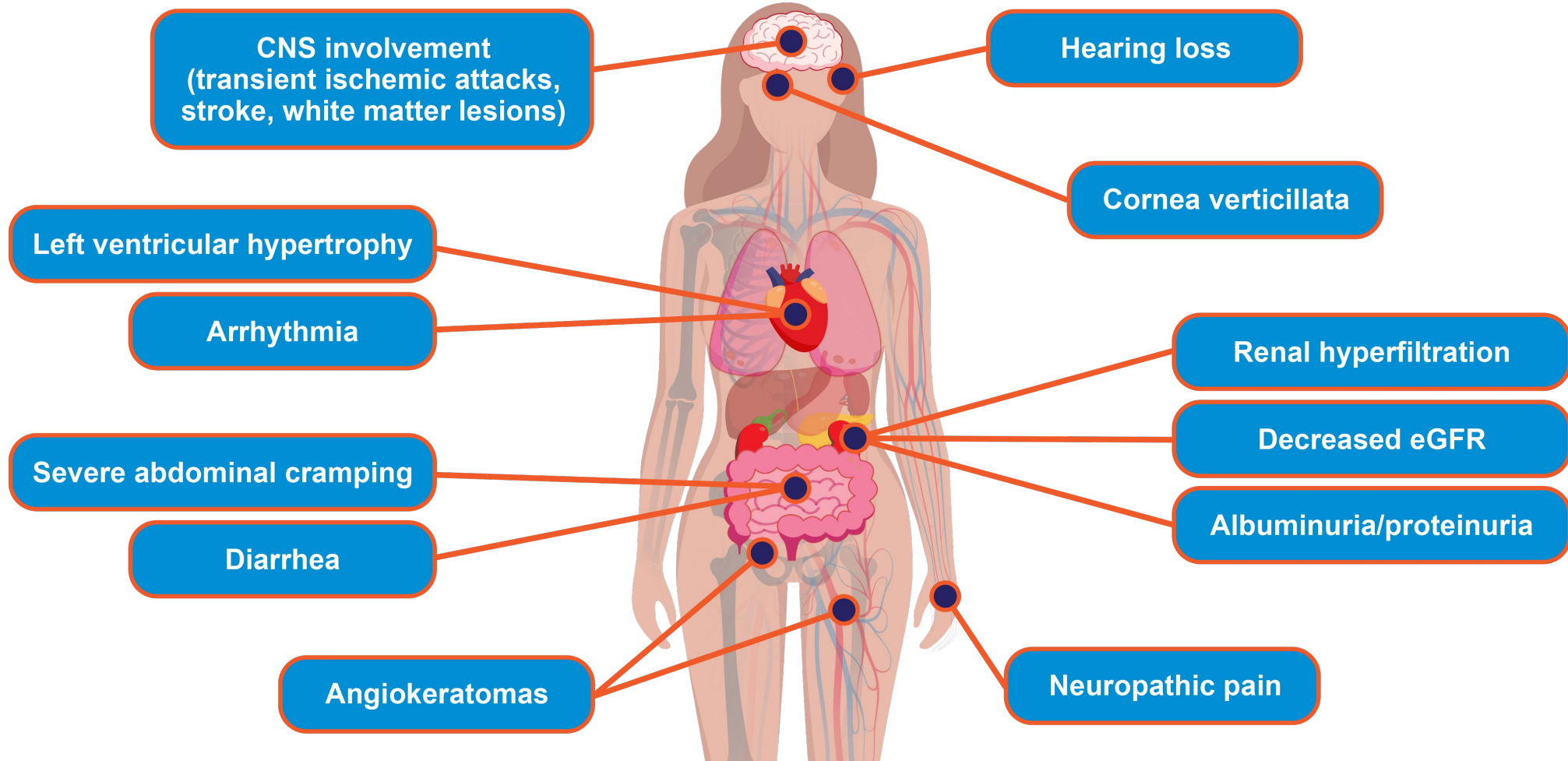
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# Background

- X-linked due to loss of function of the GLA gene
- Assumed for decades that females would be asymptomatic
- **All** daughters of affected males expected to have the same variant as their father (100% risk)
- Daughters and sons of affected females may inherit either variant from their mothers (**50% risk**)

# Signs and Symptoms of Fabry



# Findings that may differ between men and women

- Azospermia
- Age of presentation
- Age for first serious complications
- Angiokeratomas
- Sweating
- Heart disease
- Kidney disease
- Pain
- Hearing
- Vision
- Stroke
- GI symptoms
- Fatigue and sleepiness
- Depression/anxiety

# Presentation

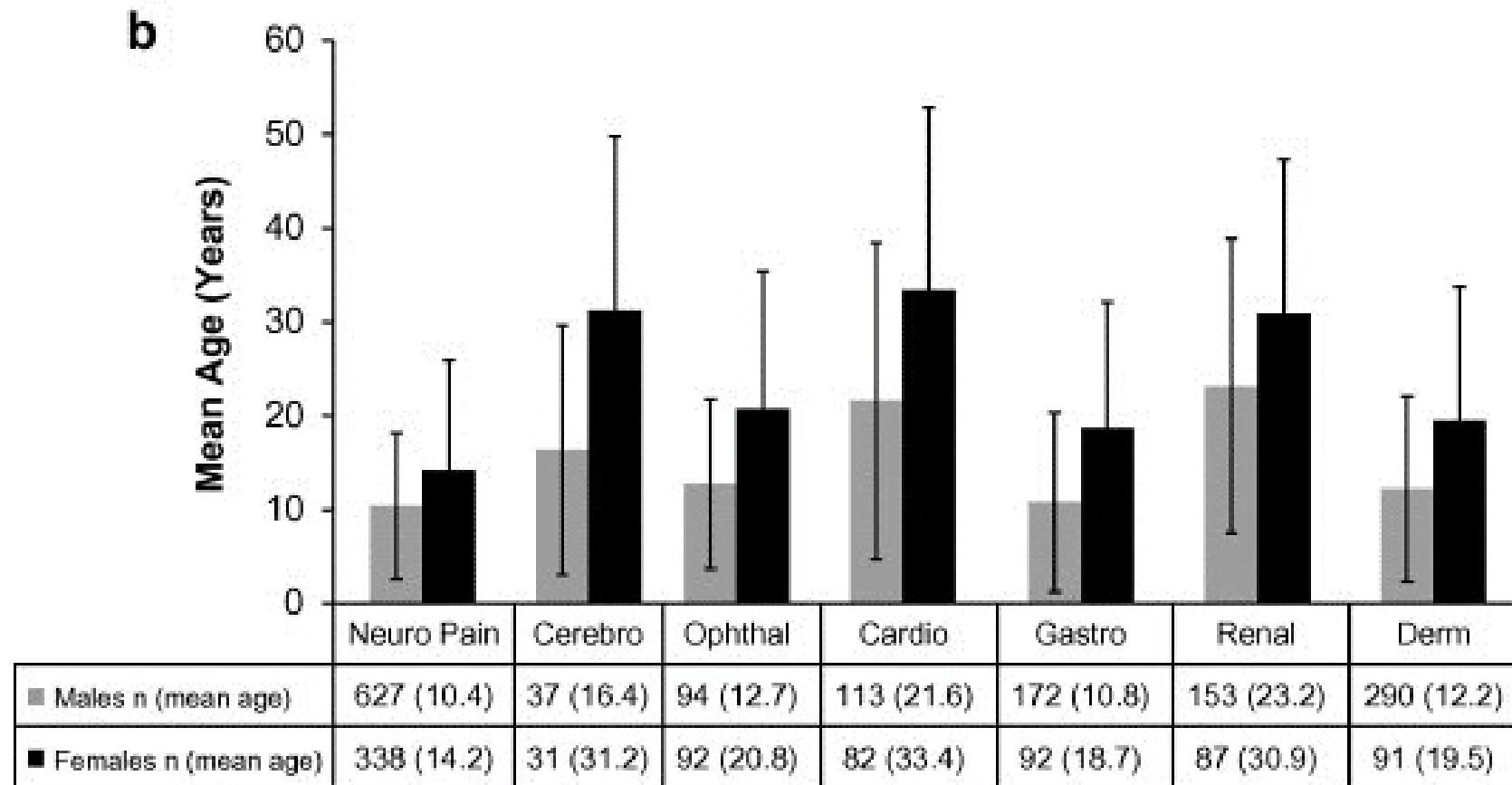
- First symptoms can be as young as age 2 years (Laney 2015)
  - BOTH SEXES
- Average age of first symptoms by passive ascertainment
  - Girls 9 years                      Boys 6 years    (Hopkin 2008)
- Adult presentation
  - Females present substantially later than men often 15 years or more

Studies from the early 2000s demonstrated 70% of females were symptomatic (classical variants)

Barba-Romero MÁ, et al. Med Clin (Barc).  
2019;153(2):47-55

- A study found that 69% of female patients considered to be asymptomatic
- In their clinical records, 68.8% indicated experiencing at least 1 symptom

# Reported age of first findings by adults





# Young adults

- Males

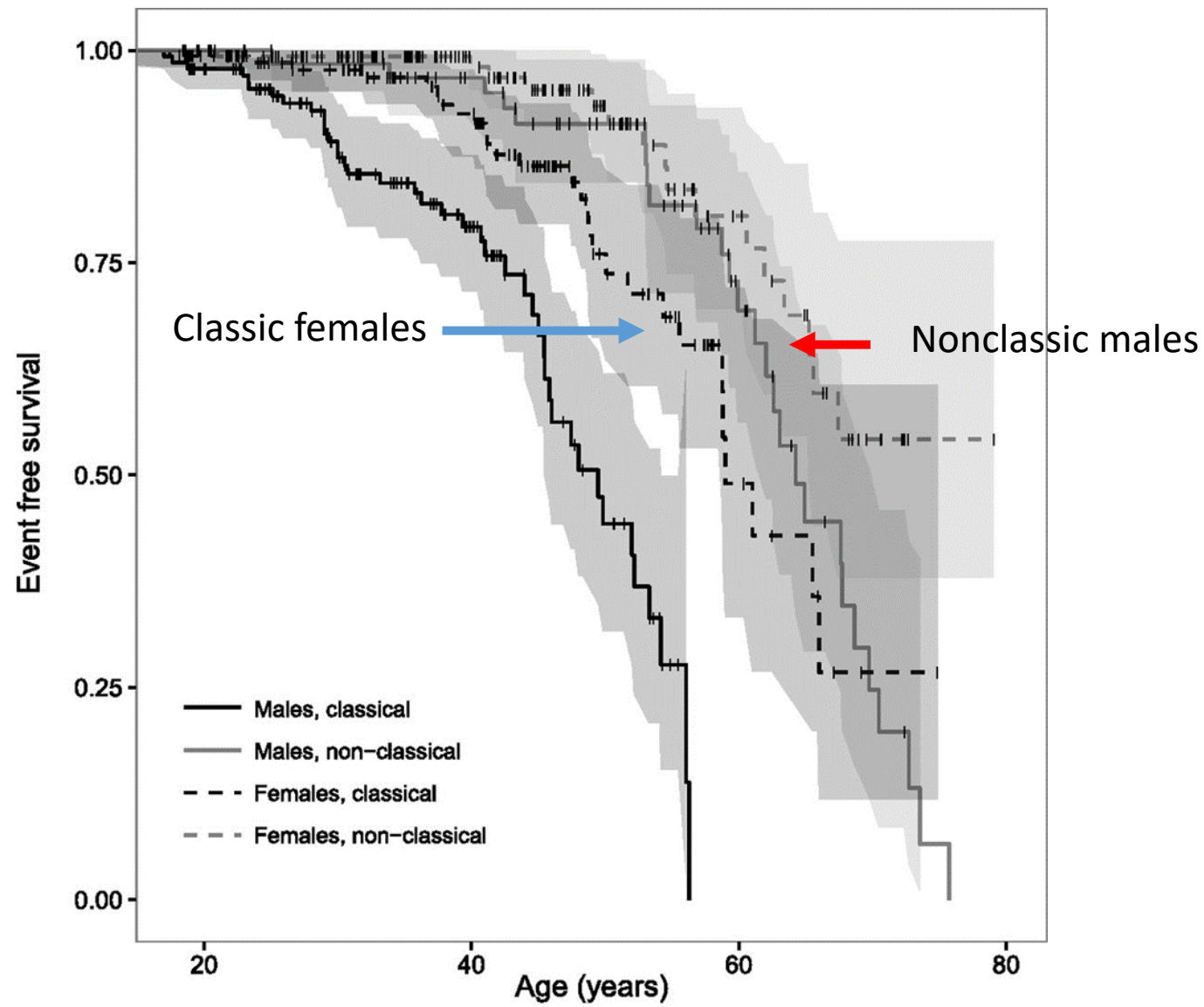
- Pain 88%
  - Crisis pain 25%
- Abdominal pain 49%
- Diarrhea 42%

- Females

- Pain 84%
  - Crisis pain 14%
- Abdominal pain 58%
- Diarrhea 44%

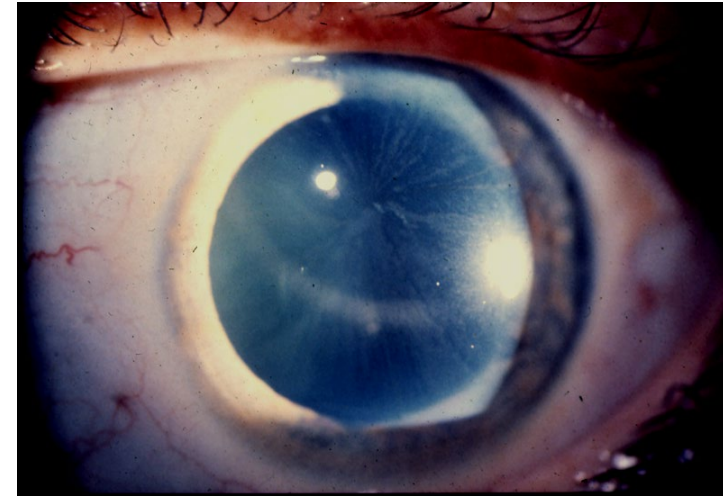
# Young adults treatment outcomes

- Males
  - Pain reduced by 7%
    - Crisis pain by 10%
  - Abdominal pain and diarrhea decreased by 7.5%
  - All of these improved more with longer time on treatment (average time 4 years)
- Females
  - Pain reduced by 7%
  - Diarrhea reduced by 12%
  - Abdominal pain and crisis pain were not statistically significant but were lower
  - Improvement was maintained but not significantly improved with longer time (too little data may explain this)



Males, classical	129	51	0	0
Males, non-classical	65	55	20	0
Females, classical	136	85	9	0
Females, non-classical	142	80	22	0

# Angiokeratoma and vision



Ophthalmologic (corneal whorls) 77% of females with >90% in males (Sodi 2007)

# Sweating

- Both men and women often report hypohydrosis and sensitivity to heat
- Abnormal sweating (both too little and too much) up to 25% of females (Ries 2003)
- Men are more likely to have anhidrosis (complete lack of sweating)
- Hyperhydrosis (sweating too much) much more common in Females
  - 12% female                      6% male

# Heart disease

Heart disease is clearly the leading cause of early death related to heart disease for both sexes

- Women
- 35% will have a serious complication related to the heart
- At least 50% of first serious complications are heart related average age 44
- Men
- 49% will have a serious heart complication
- Average age 36

59% of Female patients have active heart disease (Deegan 2009)

# Heart Disease

- Females may develop scarring in the heart without hypertrophy (up to 25%)
- This rarely happens in males
  
- This difference matters because the monitoring we do most frequently doesn't detect fibrosis well.

## Kidney disease

- First life-threatening complication in men is kidney disease (approximately 2/3 of untreated men)
- Proteinuria in their 20s and renal failure 20s to 50s
- Women have greatly elevated risk, 10% will experience significant renal disease with 4% progressing to renal failure



# Female kidney involvement

- Nearly all will have storage on kidney biopsy
- 40% with proteinuria or decreased GFR (Deegan 2009)
- 1-4% of females will go to end stage kidney disease (Waldek 2014)

# Kidney disease in Young adults and adolescents

- Kidney: 27% had data
  - UP/CR <0.5 Low renal 117
  - UP/CR >0.5 High renal 23
  - Age of treatment 20 years for LRI  
26 years for high
  - GFR loss 1.18 vs 2.39
- Kidney: 22% had data
  - low renal 59
  - High renal 7
  - Age of treatment 23 y LRI vs 28  
HRI
  - GFR loss 0.92 LRI vs. not enough  
data for HRI

# Kidney Disease

- Women have lower risk than men, but higher risk than other women
- In principle the early renal damage could lead to higher risk for renal insufficiency in later life
- No studies have looked
- This is important because women clearly need to be monitored and baseline kidney function tends to correlate with progression and severity of the other complications of Fabry disease. Thus proteinuria even if not going to end-stage renal disease may increase risk for heart, cerebrovascular and other complications.

## Cerebrovascular disease

- Men
- 6.9% will have a stroke
- Average age of first stroke 39
- Women
- 4.3% will have a stroke
- Average age of first stroke 46

77% of stroke was prior to advanced heart or renal disease. (Sims 2009)

# Cerebrovascular Disease

- The differences between Female and Male patients are not big and may not be significantly different
- Both sexes need to be followed closely and aware of the risk
- The sexes should have similar approaches to prevention, evaluation and intervention

# Other Common Findings

- Peripheral neuropathy 77.6% (Morand 2019)
- Chronic fatigue, day time sleepiness, and poor sleep at night
  - 68% mixed population with no difference between men and women (Duning 2009)
- Lymphedema 12.7% (Alkhatib 2023)
  - Mixed population of men and women
  - Not enough data to determine if there are differences
- GI symptoms (abdominal pain, recurrent diarrhea, constipation in older patients)
  - 45% abdominal pain, 39% recurrent diarrhea (Wilcox 2018)
  - Male and female are similar over all but we need more detailed data
- Hearing loss 50% of females (Keilmann 2006)

# Summary

- There are clearly differences between female and male patients
- Many of the signs and symptoms of concern are high enough risk to warrant close monitoring for both male and female patients
- If treatment is started with first symptoms or any evidence of progressive storage many patients will be on treatment and therefore require close monitoring
- There is a need for more detailed and nuanced studies in both male and female patients

# Comment on Treatment Initiation

- First symptoms can be as young as age 2 years typically around age 9 years (Laney 2015)
- Published recommendation to treat as soon as there are symptoms of any kind (Hopkin 2016, Ortiz 2018)
- Delay in diagnosis or treatment may result in irreversible tissue damage.
- Treatment response is more complete when started earlier in the course.
- Not all women will develop symptoms which complicates decision making.



Questions?