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Multicentre UK study of the natural history of 32 patients with cerebrotendinous xanthomatosis

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive lipid storage disease caused by mutations in *CYP27A1,* which encodes a mitochondrial enzyme sterol 27-hydroxylase involved in bile acid synthesis. Juvenile cataracts are an early diagnostic marker, but if untreated increased levels of cholestanol cause progressive neurologic dysfunction and pulmonary insufficiency. It is treatable with chenodeoxycholic acid if started ≤25 years of age. We present the largest UK cohort of CTX patients detailing their natural history and diagnostic pathway.



Figure 1. Tendon xanthomas on Achilles tendons (left) and extensor hand tendons (right).

METHODS

Patient data, including demographics, clinical features, age of onset, biochemical and genetic results (where available) and treatment outcomes, were compiled through a CTX working group of clinical specialists from 11 centres across the UK. Cumulative function analysis was used to assess the probability of onset of each clinical feature at any given age.

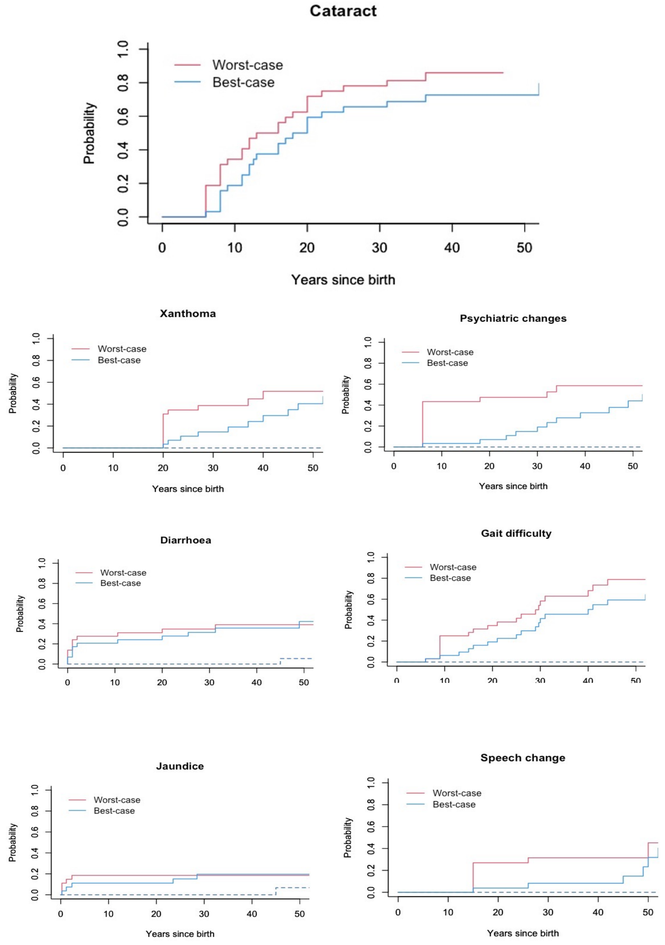


Figure 2. Cumulative incidence function analysis of common CTX clinical features. Best case and worst case scenarios were used to account for cases where the presence of the clinical feature was known but not the age of onset. Cataracts (top) are an early, frequent clinical feature of CTX, when compared to other clinical features (below).

RESULTS

Thirty-two patients from 21 families with CTX were collated; 56% were male and 61.3% were of Asian ethnicity. Age of diagnosis was 28.3 ±13.1 years (follow up 10.6 ±7.8 years). Cataracts were the most prevalent feature, occurring in 84% (27/32), presenting on average 12.6 years prior to their CTX diagnosis. Cataracts prompted CTX investigation in 37.5% (12/32) patients. Ten variants in *CYP27A1* gene were identified and mean plasma cholestanol was 88.9 ±37.5 µmol/L (normal range 1-18 µmol/L). There was a mean diagnostic delay of 9.1 years for patients (using the suspicion index for CTX). Thirty patients received treatment, mean age at start was 34.1 ±17.5 years. This was reported as beneficial in 63.3% (19/30) patients (mean age was 29.4 ±4.2 years) with improvement/halting of symptoms.

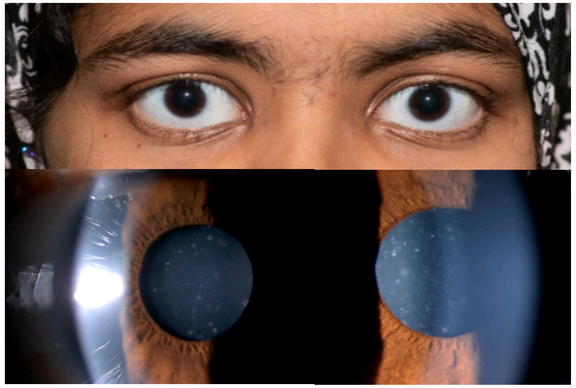


Figure 3. Female patient <20 years who presented to ophthalmology with bilateral blue dot cataracts. She was found to have a CYP27A1 mutation on cataract genetic panel testing as part of the 100,000 Genomes project and was referred to CTX specialist for management.

CONCLUSION

Early molecular diagnosis of young patients presenting with cataracts is essential to expedite diagnosis of CTX patients and initiate treatment to avoid significant morbidity and mortality.