Dear editor, I have made the following modifications according to the comments of reviewers. After the modification, I have contacted the polishing company of the initial submission to finish the polishing.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

1. Kindly discuss the neurological and MSK features of CTX on MRI briefly in discussion.

I have added the typical imaging findings of CTX as follows：

confirm the same. In addition, the biochemical diagnosis of CTX is based on the increase in serum cholestanol and urine bile alcohols levels [4]. The typical imaging findings indicating the prevalence of CTX include T2-weighted and FLAIR imaging hyperintensity in the dentate nucleus [10]. The current case supports the inclusion of high signal intensity of the two dentate nuclei on MRI as a typical feature of CTX [11].The typical imaging manifestations of CTX are high signal in T2 weighted imaging and FLAIR imaging of dentate nucleus.

2. It would be worthwhile to discuss the biochemical tests like lipid profile.

I have added the biochemical tests like lipid profile of CTX as follows：

confirm the same. In addition, the biochemical diagnosis of CTX is based on the increase in serum cholestanol and urine bile alcohols levels [4]. The typical imaging findings indicating the prevalence of CTX include T2-weighted and FLAIR imaging hyperintensity in the dentate nucleus [10]. The current case supports the inclusion of high signal intensity of the two dentate nuclei on MRI as a typical feature of CTX [11].The typical imaging manifestations of CTX are high signal in T2 weighted imaging and FLAIR imaging of dentate nucleus.

3. The resolution of MRI images is not up to the mark. If available kindly add images of higher resolution.

I have re-uploaded the high resolution MRI images as follows:

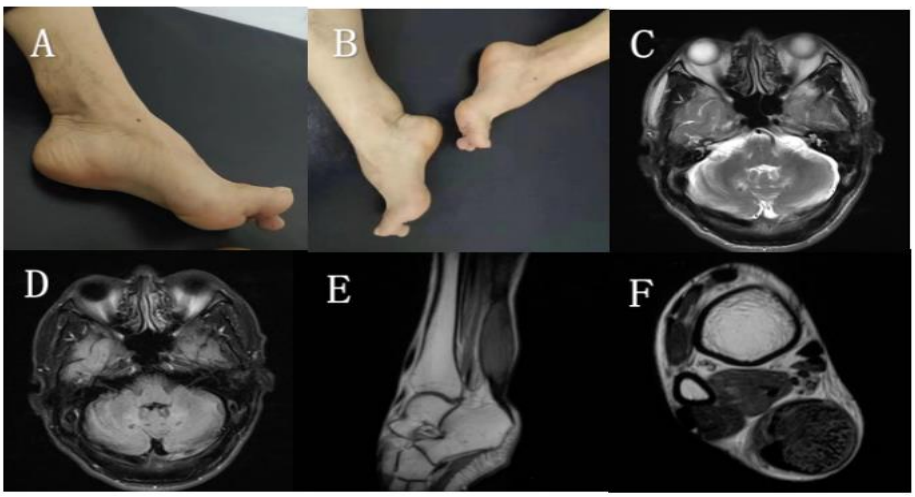

Figure A, Figure B These two pictures showed arched feet and egg-sized, hard, painless lumps in both Achilles tendons; **Figure C, Figure D** MRI of the brain showed T2-weighted and FLAIR imaging hyperintensity in the bilateral cerebellar dentate nuclei.; **Figure E, Figure F** MRI of the right ankle showed fusiform swelling and abnormal signals in the Achilles tendons.

4. If known kindly add what is the normal function of *CYP27A1* gene in human body.

I have added the normal function of *CYP27A1* gene in human body as follows:

The main cause of CTX is sterol 27-hydroxylase deficiency caused by the mutation of *CYP27A1* [3]. *CYP27A1* encodes sterol 27-hydroxylase and is the only gene known to be associated with CTX [4]. Sterol 27-hydroxylase is involved in the

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

1. Introduction: Please cite the related studies (these should be discussed at the discussion section).

I have cited the related studies as follows:

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid deposition disorder characterized by systemic signs and neurological dysfunction [1]. CTX is a treatable genetic metabolic disease, and early diagnosis and treatment can delay the progression of the disease to a considerable extent [2]. We report a case of CTX caused by mutations at two sites in *CYP27A1*. This case report will help clinicians to better understand CTX and its presentation, leading to early diagnosis and treatment, thereby improving the quality of life of patients.

REFERENCES

1 **Dell'Aversano Orabona G**, Dato C, Oliva M, Ugga L, Dotti MT, Fratta M, Gisonni P. Multi-imaging study in a patient with cerebrotendinous xanthomatosis: radiology, clinic and pathology correlation of a rare condition. BJR Case Rep 2020; **12**; 6: 20190047. [PMID: 32201602 DOI: 10.1259/bjrcr.20190047]

2 **Degrassi I,** Amoruso C, Giordano G, Del Puppo M, Mignarri A, Dotti MT, Naturale M, Nebbia G. Case Report: Early Treatment With Chenodeoxycholic Acid in Cerebrotendinous Xanthomatosis Presenting as Neonatal Cholestasis. Front Pediatr 2020; **8**: 382. [PMID: 32766184 DOI: 10.3389/fped.2020.00382]

2. Case: Please clearly elaborate why do a patient with such an almost-lifelong illness finally underwent genetic testing, even 2 years after a major surgery was done. A strong rationale must evidently be elaborated on each additional examination/investigation, not just random employment of new technology.

I have explained the reason why the patient will eventually accept genetic testing as follows:

Genetic testing

Based on the patient's medical history, clinical manifestations, and imaging analyses, it was unclear if CTX was involved, and gene sequencing was required to confirm the diagnosis. After informing the patient, the patient was eager to identify the underlying cause and had hopes for treatment; therefore he agreed to undergo gene sequencing analyses. Genomic DNA was extracted from the peripheral blood cells of the patient, and first-generation sequencing of the exon coding region of *CYP27A1* revealed that the gene had a compound heterozygous mutation of c.380G>A (Fig A1-A3, Table A1-A3) and c.1563dupA (Fig B1-B3, Table B1-B3). Further examination demonstrated that the mother and sister of the patient were carriers of the c.1563dupA mutation.

3. Discussion: Apart from CDCA, is there no other possible treatment for such a rare, devastating, and progressive disease? If none, please clearly state so.

There is no other possible treatment for such disease, I have stated it as follows:

In CTX treatment, there is currently no clear treatment plan, and the condition can be treated symptomatically based on the different clinical manifestations. Bile acid supplements, such as CDCA, provide a source of primary bile acids, which can inhibit the synthesis of bile acids through a negative feedback mechanism, thereby prevent the accumulation of cholesterol and cholestanol [12]. Consequently, early oral bile acid supplement treatment is recommended [13].In addition, cataract extraction is common performed in these patients, and xanthoma can be surgically removed.

4. Conclusion: The conclusion of "Prompt diagnosis and treatment of CTX improve patient outcomes" does NOT reflect the rather-gloomy outcome in this patient (After 1 year of treatment, the patient felt that the symptoms of weakness in both lower limbs had improved slightly); nor the 33-year duration from onset to diagnosis.

In this case, after 1 year of treatment, the patient felt a slight improvement in the weakness of both lower limbs, and the treatment effect was indeed not good. However, we believe that the treatment effect is weakened because of the delay in the clear diagnosis and implementation of treatment, which has been complicated by many systemic complications. According to the treatment process of this patient, it does not reflect the view that timely diagnosis and treatment of CTX can improve the prognosis of the patient, so we decided to delete "Prompt diagnosis and treatment of CTX improve patient outcomes" after discussion.

5. Illustrations: More comprehensive clinical pictures are absolutely needed to give the readers more insight about this rare, devastating disase.

I have added more clinical pictures as follows:

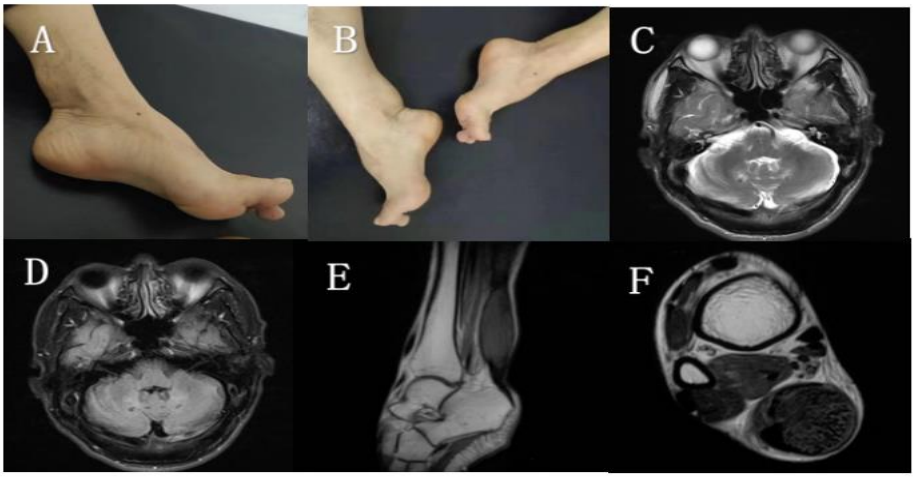

Figure A, Figure B These two pictures showed arched feet and egg-sized, hard, painless lumps in both Achilles tendons; **Figure C, Figure D** MRI of the brain showed T2-weighted and FLAIR imaging hyperintensity in the bilateral cerebellar dentate nuclei.; **Figure E, Figure F** MRI of the right ankle showed fusiform swelling and abnormal signals in the Achilles tendons.