International Journal of Advanced Research in Medicine

E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2023; 5(4): 05-10
Received: 03-06-2023
Accepted: 09-07-2023

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A brief report on a case of cerebrotendinous xanthomatosis

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DOI: https://doi.org/10.22271/27069567.2023.v5.i4a.516

Abstract
Cerebrotendinous Xanthomatosis is an uncommon autosomal recessive condition caused by a deficient enzyme in the bile acid synthesis pathway. This deficiency leads to the accumulation of cholestanol and cholesterol in various tissues, resulting in neurological, ocular, vascular, and musculoskeletal symptoms.
I will be discussing the clinical, imaging, and genetic sequence characteristics of a 33-year-old female who exhibited symptoms such as gait instability, swelling on the posterior aspect of both ankles and medial malleolus, swaying while walking, speech disturbances, and coordination issues in both upper and lower limbs for the past six months.
Imaging examinations were conducted, unveiling a range of observations consistent with Cerebrotendinous Xanthomatosis in both the brain and tendons. The diagnosis was subsequently verified through laboratory analyses and genetic sequencing.

Keywords: Cerebrotendinous xanthomatosis, cholestanol, cerebellar Hemispheres

Introduction
Cerebrotendinous Xanthomatosis is a rare autosomal recessive disorder stemming from an enzyme deficiency in the bile acid synthesis pathway leading to the deposition of cholestanol in the brain, tendons, soft tissues, and eyes, causing cerebellar dysfunction, premature cataract, and the emergence of tendon and soft tissue xanthomas.
Approximately 300 cases of Cerebrotendinous Xanthomatosis have been documented globally. The condition shows potential for treatment with chenodeoxycholic acid. Timely diagnosis and intervention are crucial to forestall the neurological consequences associated with the disease.

Case history
A 33-year-old woman presented with symptoms including gait instability, swelling on the posterior aspect of bilateral ankles and medial malleolus, swaying while walking, speech disturbances, and lack of coordination in both upper and lower limbs, persisting for the past six months.

Past history
The patient underwent cataract surgery in both eyes six years ago and has a history of incoordination in the upper limbs since the age of 10. There are reported difficulties in tasks such as mixing food, bringing food to the mouth, and inserting feet into footwear. Clinical examination revealed the presence of ataxia and soft, non-tender swelling along the posterior aspect of both ankle joints and on the medial malleolus. [Figure 1A].

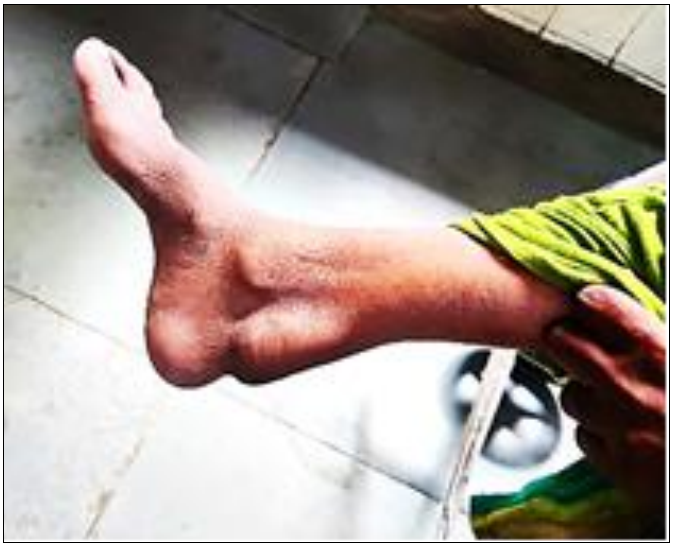


Fig 1: Tendo-achilles Xanthoma of right lower limb

X-RAY: X-ray imaging of the ankle joints disclosed soft tissue swellings along the posterior aspect of both ankle joints and the calcaneal bones. [Figure 2].

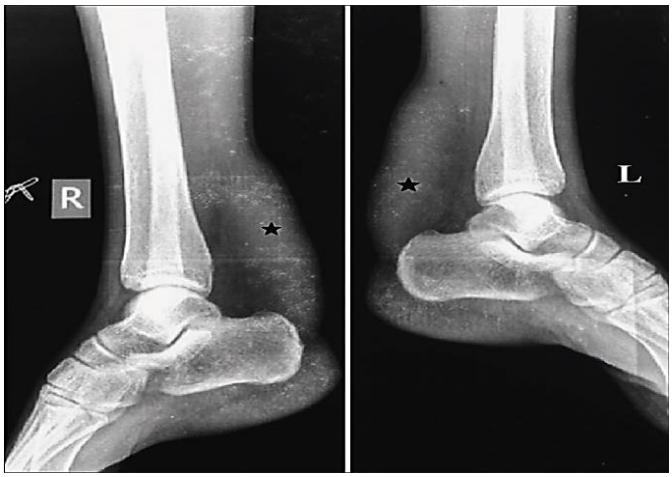


Fig 2: Soft tissue swelling of Achilles tendon on X-ray (indicated by *)

A preliminary diagnosis of cerebrotendinous xanthomatosis was established, given the observed coordination issues in both upper and lower limbs, specifically limb ataxia indicative of cerebellar symptoms. On examination, the finger-nose test yielded positive results, indicating cerebellar issues, and the dysdiadokinesia test also showed positive findings.

The knee heel test yielded positive results, and the patient was unable to perform tandem walking, which serves as a rapid screening test for vestibular disorders. No hearing loss was reported. Gait ataxia, manifested by swaying while walking, was observed.

The Romberg's test: The Romberg's test results were negative. (Romberg's test is used to measure a person's sense of balance.) The assessment indicates dysfunction in the dorsal column of the spinal cord, with observed dysarthria (bulbar symptoms). Pyramidal tract involvement is evident through spasticity, hyperreflexia, and a pendular knee jerk.

There are no sensory loss symptoms or objective sensory deficits upon examination. The absence of radicular or root pains, as well as the lack of bladder involvement, suggests no spinal cord involvement. Vibration and joint position remain normal, further supporting the exclusion of spinal cord disease.

In cases where the spino-cerebellar tracts are affected, there would typically be a loss of vibration and joint position senses. However, the presence of dysarthria suggests a more widespread cerebellar involvement, including cerebellar outflow tracts.

Blood Investigations

The lipid profile results showed a total cholesterol level of 306 mg/dl, with LDL at 205 mg/dl, VLDL at 46 mg/dl, and HDL at 55 mg/dl. Triglycerides were elevated at 526 mg/dl. Other parameters in the blood chemistry were within normal ranges. The MRI of the ankle joints demonstrated fusiform enlargement of both Achilles tendons, exhibiting a signal intensity akin to muscle and a speckled appearance on axial images, consistent with tendinous xanthomatosis. [figure 3.].

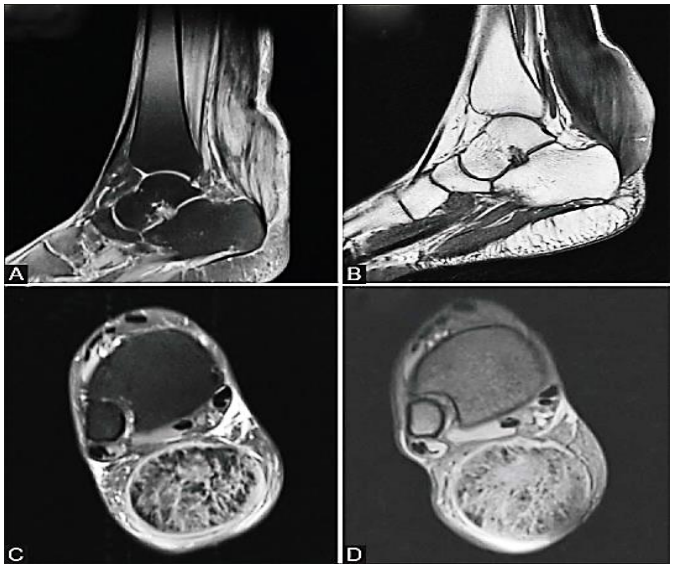
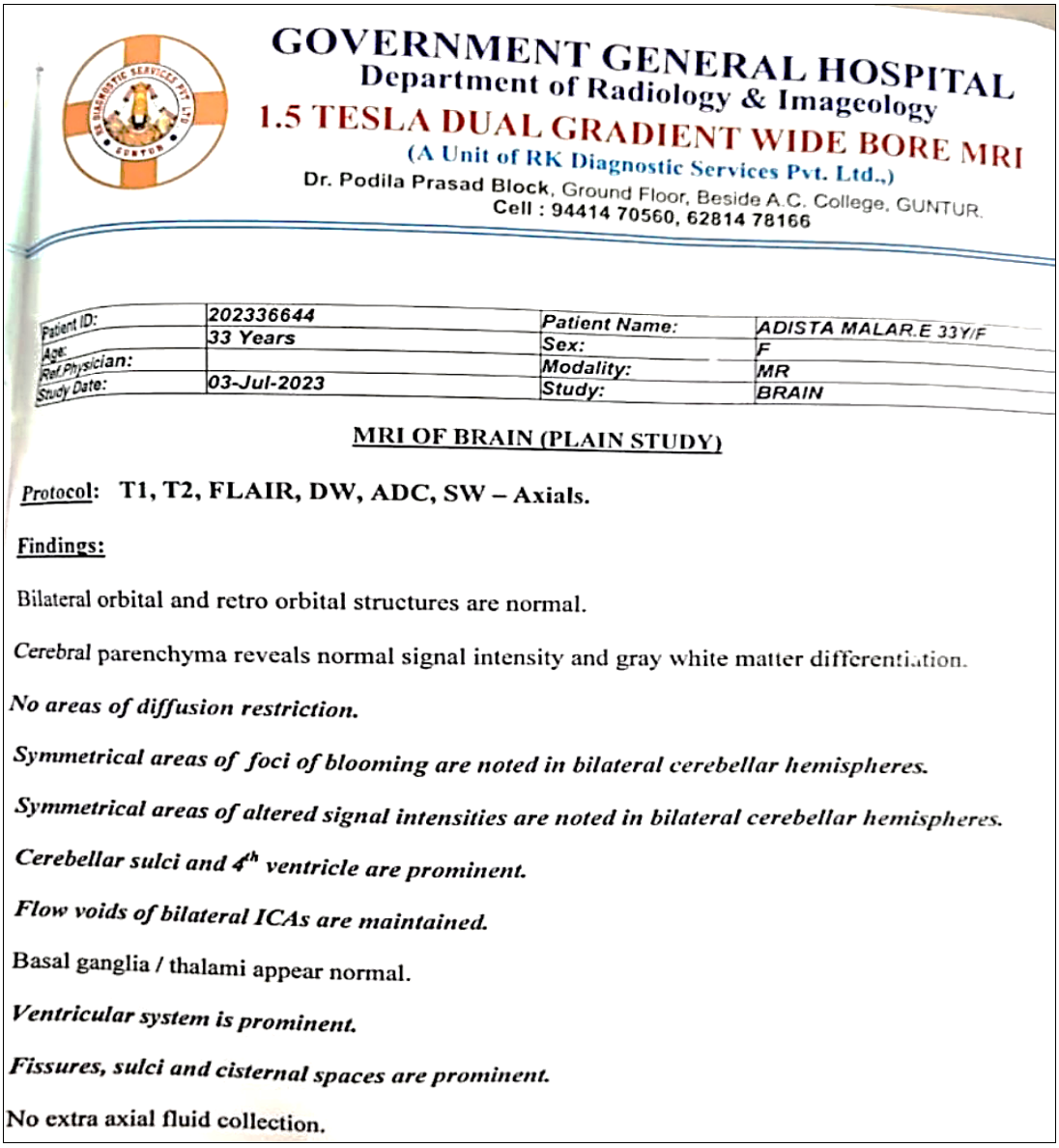


Fig 3: MRI of ankle joints

The MRI of the brain revealed symmetrical calcification in the bilateral cerebellar hemispheres, accompanied by cerebellar atrophy. Additionally, mild diffuse cerebral atrophy was observed. [Figure. 4.]



GOVERNMENT GENERAL HOSPITAL
Department of Radiology & Imageology
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Dr. Podila Prasad Block, Ground Floor, Beside A.C. College, GUNTUR.
Cell : 94414 70560, 62814 78166

Patient ID:	202336644	Patient Name:	ADISTA MALAR.E 33Y/F
Age:	33 Years	Sex:	F
Ref.Physician:		Modality:	MR
Study Date:	03-Jul-2023	Study:	BRAIN

MRI OF BRAIN (PLAIN STUDY)

Protocol: T1, T2, FLAIR, DW, ADC, SW – Axials.

Findings:

Bilateral orbital and retro orbital structures are normal.

Cerebral parenchyma reveals normal signal intensity and gray white matter differentiation.

No areas of diffusion restriction.

Symmetrical areas of foci of blooming are noted in bilateral cerebellar hemispheres.

Symmetrical areas of altered signal intensities are noted in bilateral cerebellar hemispheres.

Cerebellar sulci and 4th ventricle are prominent.

Flow voids of bilateral ICAs are maintained.

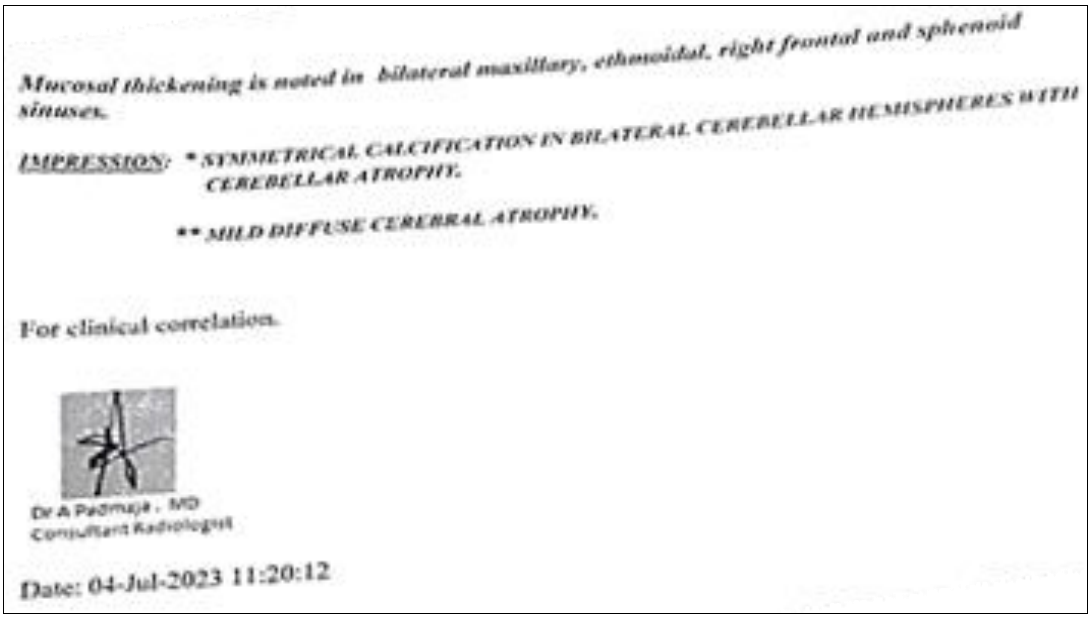
Basal ganglia / thalami appear normal.

Ventricular system is prominent.

Fissures, sulci and cisternal spaces are prominent.

No extra axial fluid collection.

Fig 4:



Mucosal thickening is noted in bilateral maxillary, ethmoidal, right frontal and sphenoid sinuses.

IMPRESSION: * SYMMETRICAL CALCIFICATION IN BILATERAL CEREBELLAR HEMISPHERES WITH CEREBELLAR ATROPHY.

** MILD DIFFUSE CEREBRAL ATROPHY.

For clinical correlation.

Dr A Padmaja , MD
Consultant Radiologist

Date: 04-Jul-2023 11:20:12

Fig 5:

Fig 4 & 5: MRI brain reporting bilateral cerebellar hemisphere calcifications

Genetic sequencing for this patient detected a mutation in exon 3 of the CYP27A1 gene. (Figure.5)

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#258/A, Bommasandra, Hosur Road, Bangalore - 560 099, India.
Tel : +91 (0)80 67154989 / 990, Web: www.medgenome.com

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DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	**YEDUKONDALA ADISTA MALAR**	Order ID/Sample ID:	**699794/8058282**
Gender:	Female	Sample Type:	Blood
Date of Birth / Age:	38 years	Date of Sample Collection:	NA
Referring Clinician:	Dr. N. V. Sundarachary, Government General Hospital - Guntur	Date of Sample Receipt:	14th July 2023
		Date of Order Booking:	17th July 2023
		Date of Report:	4th August 2023
Test Requested:	**Clinical exome**		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Ms. *Yedukondala Adista Malar,* born of a consanguineous marriage, presented with clinical indications of bilateral cataracts at 5 years of the age [surgery done], ataxia, chronic progressive cerebellar ataxia with tendon xanthomas at tendon Achilles. MRI of the brain showed cerebellar calcifications, cerebral and cerebellar atrophy. She is suspected to be affected with cerebrotendinous xanthomatosis and has been evaluated for pathogenic variations.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
CYP27A1 **(+)** (ENST00000258415.9)	Exon 3	c.601C>T **(p.Gln201Ter)**	Homozygous	Cerebrotendinous xanthomatosis (OMIM#213700)	Autosomal recessive	Likely Pathogenic **(PVS1,PM2)**

Copy Number Variants CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous nonsense variant in exon 3 of the ***CYP27A1*** gene (chr2:g.218812376C>T; Depth: 237x) that results in a stop codon and premature truncation of the protein at codon 201 (p.Gln201Ter; ENST00000258415.9) was detected (Table). The p.Gln201Ter variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomdAD (v2), topmed and in our internal databases. The *in silico* prediction# of the variant is damaging by MutationTaster2. The reference codon is conserved across species.

OMIM phenotype: Cerebrotendinous xanthomatosis (OMIM#213700) is caused by homozygous or compound heterozygous mutations in the *CYP27A1* gene (OMIM*606530). This disorder is lipid-storage disease characterized clinically by progressive neurologic dysfunction (cerebellar ataxia beginning after puberty, systemic spinal cord involvement and a pseudobulbar phase leading to death), premature atherosclerosis, and cataracts. Large deposits of cholesterol and cholestanol are found in virtually every tissue, particularly the Achilles tendons, brain, and lungs. Cholestanol, the 5-alpha-dihydro derivative of cholesterol, is enriched relative to cholesterol in all tissues. The diagnosis

CAP ACCREDITED

Fig 6:

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can be made by demonstrating cholestanol in abnormal amounts in the serum and tendon of persons suspected of being affected. Plasma cholesterol concentrations are low normal in CTX patients [PMID: 18842627].

Based on the above evidence[$], ***this CYP27A1 variation is classified as a likely pathogenic variant and has to be carefully correlated with the clinical symptoms.***

The significance/classification of the variant(s) may change based on the genetic testing in parents and other family members.

Additional Information

- No other SNV(s)/INDELS or CNV(s) that warrants to be reported were detected. All the genes covered in this assay have been screened for the given clinical indications. To view the coverage of all genes Click here. NGS test methodology details of this assay are given in the appendix.
- [$]Genetic test results are reported based on the recommendations of American College of Medical Genetics and Genomics (ACMG) [PMID: 25741868, 31690835, 32906214].
- With regard to ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (PMID: 35802134; ACMG SF v3.1), we report significant pathogenic and/ or likely pathogenic variants in the recommended genes for the recommended phenotypes, only if informed consent is given by the patient.
- Please write an email to genetic.counseling@medgenome.com in case you need assistance for genetic counselling. For any further technical queries please write an email to techsupport@medgenome.com

RECOMMENDATIONS

- Sequencing the variant(s) in the parents and the other affected and unaffected members of the family is recommended to confirm the significance.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.
- The sensitivity of NGS assay to detect copy number variants (CNV) is 70-75%. We recommend discussing alternative testing methodology options with MedGenome Tech Support (techsupport@medgenome.com) as required. In case clinician is suspecting CNV as an important genetic etiology, alternate tests like microarray/ MLPA or qPCR may be considered after discussing with the MedGenome TechSupport team.

Sandhya Nair, Ph.D	Balaji Rajashekar, Ph.D	Dr. Meenakshi Lallar, MS (Obgyn), DM (Medical Genetics)
Sr. Manager - Variant Interpretation	Director - Clinical Bioinformatics	Consultant - Clinical Geneticist

APPENDIX

Fig 7:

Fig 6 & 7: Genomic study report detecting CYP27A1 mutation in exon 3.

Discussion

Based on a comprehensive evaluation involving clinical, biochemical, radiological findings, and genetic sequencing, the diagnosis for this patient is cerebrotendinous xanthomatosis. The identified features include hypercholesterolemia, bilateral cataract, swollen Achilles tendons, and a CYP27A1 mutation in exon 3. The MRI of the brain disclosed symmetrical calcification in bilateral cerebellar hemispheres, along with cerebellar atrophy and mild diffuse cerebral atrophy.

Cerebrotendinous xanthomatosis is an uncommon inherited lipid storage disorder marked by the abnormal accumulation of cholestanol and cholesterol in various tissues, predominantly in the brain and tendons. This condition is defined by a deficiency in the sterol 27-hydroxylase enzyme, crucial for converting cholesterol into bile acids, namely cholic and chenodeoxycholic acid. A deficiency in this enzyme pathway leads to the accumulation of bile acid precursors, specifically cholestanol and bile alcohols. Elevated levels of cholesterol and cholestanol deposit abnormally in soft tissues, resulting in premature cataract formation, the development of soft tissue and tendon xanthomas, and early atherosclerosis. The neurological spectrum of the disease encompasses subnormal intelligence, learning difficulties, cerebellar dysfunction, and neuropathy.

Cerebrotendinous xanthomatosis is characterized by elevated serum levels of cholesterol and cholestanol. Mutations in CYP27A1 result in a deficiency of sterol 27-hydroxylase, a key enzyme in the conversion of cholesterol to the bile acid chenodeoxycholic acid. This enzymatic deficiency impedes the synthesis of chenodeoxycholic acid, leading to the accumulation of bile acid pathway intermediates and cholestanol in the bloodstream and tissues of affected individuals. The equilibrium between the synthesis and catabolism of cholesterol is crucial for maintaining normal cellular processes. In Cerebrotendinous xanthomatosis, clinical manifestations typically emerge in infancy and progress through the first and second decades of life. Patients with this condition exhibit a broad spectrum of manifestations, involving multiple organs and presenting with diverse neurological and non-neurological symptoms.

Neurological characteristics documented in the literature for Cerebrotendinous xanthomatosis encompass pyramidal and cerebellar signs, sensory-motor peripheral neuropathy, intellectual disability, and dementia. Non-neurological disorders commonly observed include early-onset bilateral cataracts in childhood, the development of tendon xanthomas (primarily in the Achilles' tendons), and diarrhea. The diagnosis of Cerebrotendinous xanthomatosis is established through a comprehensive evaluation, incorporating clinical findings, biochemical testing, neuroimaging, and molecular genetic analysis.

Conclusion

The presence of early age bilateral cataracts with bilateral tendo-Achilles xanthomas and features of cerebellar dysfunction, should raise a possibility of cerebrotendinous xanthomatosis. Early diagnosis and initiation of treatment with chenodeoxycholic acid is crucial for halting further neurodegeneration.

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How to Cite This Article

Dr. Kondepudi S. A brief report on a case of Cerebrotendinous Xanthomatosis. International Journal of Advanced Research in Medicine. 2023;5(4):05-10.