A Unique Presentation of CMTX1: Factors in Diagnostic Delay and Opportunities for Improved Care

Nathaniel Wooten[1], Sheng-Che Hung[2], Daniel S Malawsky[3], Steven P Trau[1], and Yael Shiloh-Malawsky[1]

Departments of Neurology[1] and Radiology[2], University of North Carolina; Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, UK[3]

UNC DEPARTMENT OF NEUROLOGY

Poster #243

Background

- Charcot-Marie-Tooth, X-linked dominant (CMTX1), is a rare genetic condition caused by a gap junction beta protein 1 (GJB1) gene mutation.
- It is the second most common hereditary neuropathy behind CMT1A
- It typically presents with gait difficulties and loss of achilles reflex. These symptoms are typically more pronounced and have earlier onset in male patients.
- A rare presentation of CMTX1 is CNS phenotype - episodes of transient neurological dysfunction and reversible brain MRI abnormalities resembling other neurological disorders, such as stroke, demyelinating disease, or mitochondrial disorders
- These disease mimics often lead to delayed diagnosis and unnecessary tests and treatments.

Objective

- We aim to add two additional cases to the literature, investigate factors associated with diagnostic delays in CMTX1 patients with CNS phenotype and identify opportunities to shorten the process.

Methods

- We describe two new, not previously published, CMTX1 cases presented with CNS phenotype.
- We added the two patient cases to 47 other previously described cases of CMTX1 that had transient neurologic deficits.
- We compared demographic, history, exam and test result variables with time to diagnosis using a Fisher's exact test, statistical significance defined as p-value of </= 0.05.
- We evaluated association between the binary variables, such as delayed diagnosis (greater than 1 year from symptom onset), and early onset of disease (<10 years of age).

Case Presentations

Case 1: 13 year old male presented with 2 lifetime events of transient facial weakness, dysarthria, quadriparesis and areflexia lasting 12 hours.

- He had reversible diffusion weighted image changes on MRI.
- He was offered steroids at both presentations for a consideration of acute demyelinating encephalomyelitis, which his parents declined without a definitive diagnosis
- The delay to diagnosis was 5 years.

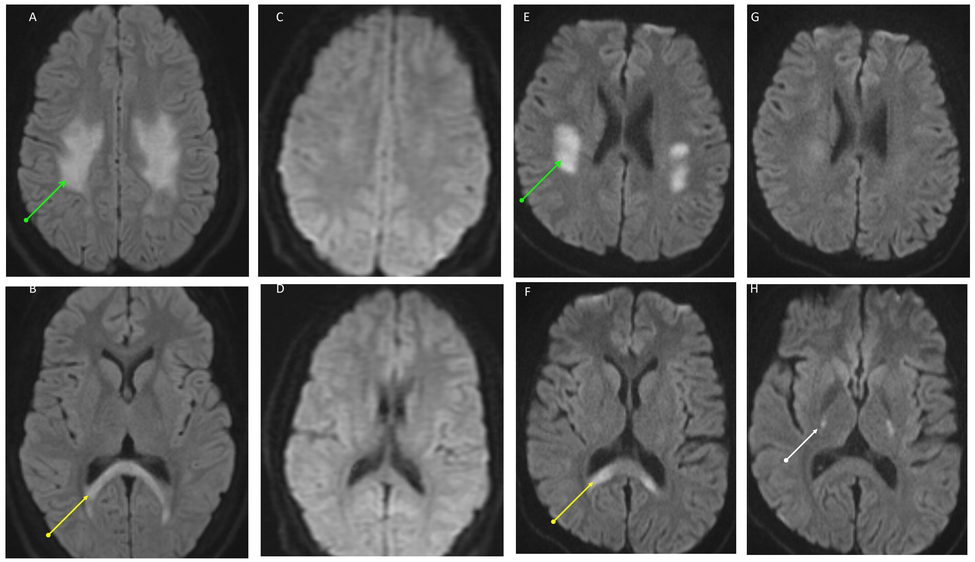
Case 2: 18 year old male that presented with first transient episode of left face and upper extremity weakness and numbness in addition to dysarthria.

- His symptoms resolved within 72 hours.
- There was no delay in diagnosis.

Figure 1

Case 1 (A-D) MRI brain, Diffusion Weighted Image (DWI): (A&B) Demonstrate DWI restricted diffusion in deep white matter (green arrow) and splenium (yellow arrow), respectively at time of symptoms. (C&D) Demonstrate near complete resolution of diffusion restriction.

Case 2 (E-H) MRI brain, Diffusion Weighted Image (DWI): (E&F) Demonstrate DWI restricted diffusion in deep white matter (green arrow) and splenium (yellow arrow), respectively at time of symptoms. (G&H) Demonstrate near complete resolution of diffusion restriction. (H) There is new restricted diffusion in the posterior limbs of the corticospinal tracts bilaterally (white arrow).



Results

- Among 49 reported cases, there was an 8-year average delay in diagnosis. This ranged from 0 to 38 years.
- Factors significantly associated with delayed diagnosis included age younger than 10 years at onset ($p<0.01$) and absence of limb weakness ($p=0.05$).
- In patients with an age of onset below 10 years, 90% had delayed diagnosis, compared to 38% of patients with symptom onset after 10 years of age.
- Two females had a delay in diagnosis of 7 and 21 years, but this is not statistically significant due to the small sample size.
- All four patients without limb weakness at presentation had a delay in diagnosis, but the small sample size limited significance.

Conclusions

- Diagnosing CMTX1 in the setting of its rare CNS phenotype is often delayed.
- Recognizing the unique clinical combination of symptoms, signs, and MRI findings can lead to earlier diagnosis and result in improved management and genetic counseling.
- The association of younger age of onset with delayed diagnosis underlines the need to raise awareness of this condition among pediatric neurologists.
- This report, at the CNS annual meeting, is aimed to increase awareness of this entity among the target audience of pediatric neurologists.

References

1. Abrams CK. GJB1 Disorders: Charcot-Marie-Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes. 1998 Jun 18 [Updated 2020 Feb 20]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
2. Lu YY, Lyu H, Jin SQ, Zuo YH, Liu J, Wang ZX, Zhang W, Yuan Y. Clinical and Genetic Features of Chinese X-linked Charcot-Marie-Tooth Type 1 Disease. Chin Med J (Engl). 2017 May 5;130(9):1049-1054.
3. Tian D, Zhao Y, Zhu R, Li Q and Liu X. (2021), Systematic review of CMTX1 patients with episodic neurological dysfunction. Ann. Clin. Transl. Neurol., 8: 213-223.
4. Gordon E, Fanadka F, Atamna A, Gour A, Brahms-Tamir B, Kinani H, Frenkel-Manzur N, Zaltzman R, Elefant E, Kestenbaum M, Levin G, Lev N. (2021). Stroke-Like Episodes in Charcot-Marie-Tooth X1 (CMTX1) Disease. International Journal of Medical Science and Clinical Invention. 8. 5299-5301.

NW reports no disclosures; SCH reports no disclosure; SPT reports no disclosures; DM reports no disclosures; YSM reports no disclosures