schedule. The second infant diagnosed with IOPD is CRIM-negative based on the two *GAA* variants identified. Initial CK level was 685 U/L and echocardiogram noted borderline left ventricular and mild right ventricular hypertrophy. He underwent immune tolerance induction (ITI) with rituximab, oral methotrexate, and IVIG with dosing per published guidelines, and he was started on Lumizyme 40 mg/kg weekly at 3 weeks of age. After 2 months on treatment, his CK level normalized to 119 U/L; he continues to have borderline LVH on repeat echocardiograms, though LVM/height (2.7) has decreased from 114.79 to 83.91. Weight gain slowed during ITI which we attributed to increased vomiting while taking methotrexate; this has since resolved.
Six infants were diagnosed with LOPD. We arranged for regular surveillance including evaluation by a neuromuscular specialist and a physical therapist every 3 months, baseline echocardiogram, regular measurement of CK levels, and referral to speech therapy for swallow evaluation in infants with clinical concern. One infant was transferred to a local genetics department after relocating out of state. Interestingly, we found that the (Cr/Crn)/GAA ratio on the dried blood spot correlated with the severity of features in most LOPD infants. Those with a higher ratio, closer to that of our IOPD infants, tended to present with earlier symptoms. One infant has been started on Lumizyme following the development of borderline left ventricular hypertrophy, with LVM/height (2.7) increasing from 51.38 to 76.48 between initial and second echocardiograms. This has resolved since starting treatment. She has three variants in the *GAA* gene, and we continue to investigate whether this may play a role in her accelerated presentation. Two infants have persistent mild elevations of CK but have not started treatment yet: one is age 1 year with CK level persistently 500 U/L, and one is <1 year old with CK levels persistently 200-300 U/L. Both infants have normal strength/development and echocardiograms, so we have elected to monitor closely. The other two infants have been completely asymptomatic with normal CK levels and echocardiograms.
Conclusion: There is a consensus on the importance of starting Lumizyme +/- ITI in newborns with IOPD as quickly as possible, ideally no later than 4 weeks old due to strong data supporting increased survival and decreased motor impairment. We achieved this goal by communicating early with our outpatient infusion center for planning and utilizing the charitable access program to provide drug while working on insurance prior authorization and appeals. We noticed a lack of strong data regarding the appropriate time to start Lumizyme in infants with LOPD showing early symptoms. This is important for future study; given that we know infants with IOPD can suffer from irreversible muscle damage, we want to ensure that the window of optimal treatment in infants with LOPD, which is much less well defined, is not missed.

https://doi.org/10.1016/j.gim.2022.01.064

eP027

Screening for co-incident *TANGO2* related metabolic encephalopathy and arrhythmia syndrome in 22q11 deletion syndrome

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Introduction: *TANGO2*-related metabolic encephalopathy and arrhythmia syndrome (TRMEA) is a recently reported autosomal recessive disorder that is characterized by episodic movement disorders, developmental delay, and recurrent metabolic crises. Metabolic crises include rhabdomyolysis, seizures, encephalopathy, lactic acidosis, hyperammonemia, and hypoglycemia, during which patients are at risk of QTc prolongation and life-threatening cardiac arrhythmias. Because of the recent discovery of this disorder, limited awareness among providers, and phenotypic variability among patients, TRMEA is likely under-recognized. Importantly, conservative management of these patients can prevent metabolic crises or lessen the complications.
Identifying a second rare genetic syndrome can often be difficult, as has been previously demonstrated in 22q11.2 deletion syndrome (22q11.2 DS) patients. Patients with 2 separate genetic syndromes are best identified by atypical presentations or differing symptoms compared to the primary/first identified genetic syndrome. *TANGO2* is located within the critical region of 22q11.2 microdeletion. Therefore, all 22q11.2 DS are hemizygous for a pathogenic deletion of the *TANGO2* gene and are at higher risk of this life-threatening disorder. Therefore, we conducted a retrospective review of all patients in the University of Michigan Health System with 22q11.2 DS for atypical presentations that could be indicative of co-incident TRMEA, followed by targeted testing of the identified individuals considered to have a moderate to high likelihood of co-incident TRMEA.
Methods: The Electronic Medical Record Search Engine (EMERSE) was used to search all 2,772,611 local digitized patient records from 1900 through 1/31/2020. Rich text patient records were initially screened for 22q11.2 DS paired with search terms for phenotypic features of TRMEA that are atypical of 22q11.2 DS. These atypical clinical course features included 4 conditions: rhabdomyolysis, cardiomyopathy, arrhythmia, and ataxia. The identified patients had their charts reviewed for molecularly confirmed 22q11.2 DS. If 22q11.2 DS was confirmed, the charts were reviewed for the identified atypical clinical course feature. Patients were then classified as low, moderate, or high likelihood of having co-incident TRMEA based on number of overlapping atypical course features and feature strength. Those with moderate to high likelihood of co-incident TRMEA were contacted for clinical genetic evaluation and targeted testing based on clinical evaluation.
Results: There were 60 patients with molecularly confirmed 22q11.2 DS who screened positive for 1 or more atypical clinical features concerning for TRMEA. One patient with known co-incident 22q11.2 DS and TRMEA was identified with each of the atypical feature screening, serving as a methodologic control and excluded from subsequent analysis. Of the remaining 59 patients, 6 were categorized as high likelihood, 14 as moderate likelihood, and 38 as less than moderate likelihood. 11 patients were deceased with 6 of the 11 being categorized as moderate (3) to high (3) likelihood of TRMEA which may have contributed to their death. Three of 59 had rhabdomyolysis, 23/59 had a ventricular arrhythmia, 13/59 had evidence of cardiomyopathy, and 23/59 had intermittent ataxia or a non-specific movement disorder. Contact was attempted for the 14 of the living patients with moderate to high likelihood of co-incident TRMEA. Seven of these patients were seen in clinic with subsequent targeted testing for *TANGO2* performed. All testing for these 7 patients were found to have a second normal *TANGO2* allele.
Conclusion: Identification of a second genetic syndrome can be challenging. Screening for atypical features of TRMEA within a 22q11.2 DS population was able to identify a known control case of co-incident TRMEA but was unable to reveal additional co-incident 22q11.2 DS patients affected by TRMEA. Though limited by a small number of patients with moderate to high categorized risk of TRMEA, these findings demonstrate the challenges of retrospective screening through the electronic medical record. This highlights the importance of screening for atypical features within at-risk populations at the time of clinical evaluation.

https://doi.org/10.1016/j.gim.2022.01.065