Case Report: Previously Undescribed Increased Alpha Fetoprotein and Thrombocytopaenia in TARP Syndrome and Reviewing its Label as a Fatal Neonatal Syndrome

Michael Lane[1]; Nicholas Allen[1]; Johannes Letshwiti[2]
1 Paediatrics, National University Ireland, Galway, 2 Paediatrics, Galway University Hospital, Galway

INTRODUCTION

- TARP (talipes equinovarus, atrial septal defect, Robin sequence, persistent left superior vena cava) syndrome is an X-linked disorder secondary to RBM10 gene mutations first described in 1970[1, 2].
- 26 cases reported in the literature to date.
- Wide interpatient phenotypic variability
  - Major features→severe cognitive, motor and language delays, brain malformations, neurological symptoms, airway/pulmonary abnormalities, failure to thrive and dysmorphism.[3]

AIMS

We present the case of a toddler diagnosed with TARP syndrome due to a splicing mutation c.2295+1G>A in the *RBM10* gene. We aimed to discuss the novel features seen in our case, the prevalence of previously described major, minor and additional disease characteristics and quantify previously reported mutation types comparing with survival beyond 1.5 yrs.

OUR CASE

Birth History

- Our patient was a dichorionic-diamniotic (DCDA) twin male born at 36 weeks by emergency C-section dues to severe IUGR
- Birth Weight was 1.86kg (0.4th centile), birth length 36.5cm(0.4th centile) and birth head circumference 32.5cm (25th centile).

Neonatal and Early Infancy

- Admitted to NICU for respiratory distress, low birth weight, hypoglycaemia and central hypotonia
- Thrombocytopaenia- 76x10^{9} /L(DOL 1) → 118x10^{9}/L(DOL 3) → 28x10^{9}/L(DOL 4)→ levels normalized post platelet transfusion.
- Conjugated Hyperbilirubinaemia- Total SBR 121umol/L and direct 69umol/L , ALP 425 U/L and GGT 483 U/L seen around 24 hrs of age. Direct bilirubin peaked at 87 on DOL16 and persisted until 4 months of age.
- Unexplained massively elevated Alpha-fetoprotein- 84,000 at DOL 31. No source of AFP was established.
- Dysmorphic features- low set ears, prominent columella, micrognathia and hypertelorism.

INVESTIGATIONS AND DIAGNOSIS

- TARP syndrome was diagnosed by single exome sequencing which found a novel de novo splicing variant/ mutation (c.2295+1G>A) in RBM10.
- Echocardiography: moderate ASD with left ventricular hypertrophy. Abdominal US: crossed fused ectopic left kidney and absent right kidney. No liver or gallbladder abnormalities.
- Other diagnostic tests completed were normal → karyotyping, CGH microarray, TORCH screen, extensive metabolic screen (serum amino acids, ammonia, urine organic acids, very long chain fatty acids, 7-deoxycholesterol levels and transferrin isoform screen).

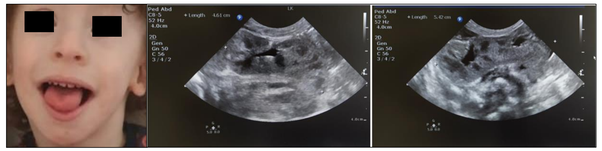

Figure 1: left-dysmorphic features (low set ears, prominent columella, micrognathia and hypertelorism. Centre and right- absent right kidney and crossed fused ectopic left kidney.

DISCUSSION

TARP syndrome has a broad phenotype with significantly interpatient variability. This has made it difficult to quantify features of the disease and predict patient outcomes. Whole exome sequencing has been a vital tool for diagnosis. Previously, Kumps et al had classified the major, minor and additional features of the disease.[3] We included our case and stratified features based on patient survival.

Unique features: 3 unique characteristics not previously seen in the syndrome- Extremely elevated AFP, thrombocytopaenia and persistent direct hyperbilirubinaemia. Given uniqueness of both AFP and hyperbilirubinaemia in this case a link was suspected. However, no congenital abnormalities likely to cause cholestasis were found on imaging. It would be atypical to see such increased levels solely secondary to jaundice.[4] Hyperbilirubinaemia was attributed to sludge gallbladder and use of TPN in the neonatal period.

Good Outcome: Originally, TARP syndrome was viewed as a fatal neonatal syndrome.[2] Recent cases and ours prove this prognosis to be untrue with Højland et al describing the first adult patient.[3, 5] Our patient has survived beyond 3 years of age and has a milder phenotype than many cases described. He suffers from a splicing mutation. Both other patients who have had a splicing mutations and both who have had inframe deletions survived beyond 18 months. Previously, Imagawa et al had seen a much milder phenotype in the only patient identified with a missense deletion.[6]

RESULTS

Table 1: Major, minor characteristics of TARP Syndrome using survival time as a case severity marker (where reported)

	Current Patient	Patients surviving <18mths (17[1])	Patients surviving >18mths (9[1])		Current Patient	Patients surviving <18mths (17[1])	Patients surviving >18mths (9[1])
Major features (100%)				**Minor features (>80%)**			
Severe cognitive delay	+	100% (4/4)	100% (8/8)	Structural cardiac abnormalities	+	88% (14/16)	100% (9/9)
Severe motor delay	+	100% (2/2)	100% (8/8)	*Atrial septal defect*	+[1]	60% (9/15)	56% (5/9)
Severe language delay	-	100% (1/1)	85% (6/7)	*PLSVC*	-	50% (7/14)	57% (4/7)
Brain malformations	+	100% (7/7)	100% (8/8)	*Additional cardiac malformations*	+[1]	83% (5/6)	75% (6/8)
Cerebellar hypoplasia	-	3/5 (60%)		Limb anomalies	-	94% (15/16)	78% (7/9)
Neurological symptoms	+	100% (4/4)	100% (8/8)	*Clinodactyly*	-	100% (1/1)	57% (4/7)
Hypotonia	+	100% (4/4)	87.5% (7/8)	*Syndactyly*	-	75% (6/8)	50% (4/8)
Airway/pulmonary abnormalities	+	100% (8/8)	100% (6/6)	*Talipes equinovarus*	-	69% (11/ 16)	33% (3/9)
Pulmonary hypoplasia	-	100% (2/2)	33% (2/6)	Postnatal growth delay	+	100% (2/2)	86% (6/7)
Respiratory insufficiency	+	100% (5/5)	80% (4/5)	*Postnatal microcephaly*	-	80% (4/5)	56% (5/9)
Failure to Thrive (FTT)	+	100% (3/3)	100% (6/6)	Skeletal abnormalities	-	82% (14/17)	78% (7/9)
with gastrostomy	-	100% (3/3)	83% (5/6)	Gastrointestinal abnormalities	+	100% (6/6)	60% (3/5)
Dysmorphism	+	100% (8/8)	100% (8/8)	*Cholestasis*	+	NR	100%[4] (1/1)
Posteriorly rotated ears	-	100% (3/3)	71% (5/7)	**Additional features (>60%)**			
Underdevelopment of alae nasi	-	80% (4/5)	75% (6/8)	Genital malformations	+	83% (5/6)	75% (6/8)
Low set ears	+	100% (7/7)	67% (6/9)	*Cryptorchidism*	+	67% (4/6)	57% (4/7)
Hypertelorism	+	86% (6/7)	75% (6/8)	Renal abnormalities	+	83% (5/6)	60% (3/5)
Wide mouth	+	80% (4/5)	75% (6/8)	Vision impairment	+	50% (2/4)	86% (6/7)
Round face	-	83% (5/6)	50% (4/8)	Hearing loss	+	100% (3/3)	50% (4/8)
Large fontanels	-	100% (3/3)	25% (1/4)	Low Platelets	+	NR	100%[4] (1/1)
Downturned mouth corners	-	80% (4/5)	50% (4/8)	Increased AFP	+	NR	100%[4] (1/1)
High/narrow palate	-	100% (2/2)					
Robin sequence (CP or M)	+	82% (14/17)	100% (9/9)				
Prominent columella	+	25% (1/4)	75% (6/8)				

CONCLUSIONS

- Whole Exome Sequencing is a powerful tool in the diagnosis of rare syndromes such as TARP syndrome. The new features seen in these cases help establish a comprehensive phenotypical picture of the disease.
- The original viewpoint of TARP syndrome as a fatal neonatal syndrome has already been heavily challenged in the literature and needs to be examined. Evidence now shows that patients with splicing and missense mutations and inframe deletions have very strong chances of thriving past this stage.

REFERENCES

1. Gorlin RJ, Červenka J, Anderson RC, Sauk JJ, Bevis WD. Robin's Syndrome: A Probably X-Linked Recessive Subvariety Exhibiting Persistence of Left Superior Vena Cava and Atrial Septal Defect. American Journal of Diseases of Children. 1970 Feb 1;119(2):176–8.
2. Johnston JJ, Teer JK, Cherukuri PF, Hansen NF, Loftus SK, Chong K, et al. Massively Parallel Sequencing of Exons on the X Chromosome Identifies RBM10 as the Gene that Causes a Syndromic Form of Cleft Palate. The American Journal of Human Genetics. 2010 May 14;86(5):743–8.
3. Kumps C, D'hoenens E, Verguit S, Lesu J, Coster R van, Jansen A, et al. Phenotypic spectrum of the RBM10-mediated intellectual disability and congenital malformation syndrome beyond classic TARP syndrome features. Clinical Genetics. 2021;99(3):449–56.
4. National Pirogov Memorial Medical University, Vinnytsia, Ukraine, Mazur OH, Yablon OS, National Pirogov Memorial Medical University, Vinnytsia, Ukraine, Rubina OS, National Pirogov Memorial Medical University, Vinnytsia, Ukraine. Alpha-fetoprotein as a biochemical diagnostic and prognostic marker for prolonged jaundice in newborns. UkrBiochemJ. 2019 Sep 13;91(5):63–9.
5. Højland AT, Lolas I, Okkels H, Lautrup CK, Diness BR, Petersen MB, et al. First reported adult patient with TARP syndrome: A case report. American Journal of Medical Genetics Part A. 2018;176(12):2915–8.
6. Imagawa E, Konuma T, Cork EE, Diaz GA, Oishi K. A novel missense variant in RBM10 can cause a mild form of TARP syndrome with developmental delay and dysmorphic features. Clinical Genetics. 2020;98(6):606–12.