Case report

THROMBOCYTOPENIA WITH ABSENT RADII (TAR) SYNDROME IN NEWBORN: A CASE REPORT

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ABSTRACT

Thrombocytopenia absent radius (TAR) syndrome is rare genetic disorder characterized by bilateral absence of the radius in each forearm with the presence of the thumb and thrombocytopenia. TAR syndrome abnormalities include various systems including skeletal, hematologic and malformations of the heart, kidneys and gastrointestinal tract.

We present a female newborn born in 35 week of gestation from the first uneventful pregnancy of juvenile mother, with birth weight of 2,550 grams. On physical examination was noted facial dysmorphia, bilateral short upper and lower limbs, palpable one bone on forearm, radial club hand and flexion against the palm, flexion of the legs at the knees and pedes equinovari. Complete blood count revealed thrombocytopenia (39x109/L). We performed X-ray of upper limbs, which suggested absence of bilateral radius bone. Head, abdominal and urinary tract ultrasound were normal. Heart ultrasound proofed foramen ovale and myocardial hypertrophy. Genetic analysis showed microdeletion in 1q21.1, which confirmed our suspected diagnosis of TAR syndrome.

Patients with TAR syndrome require a multidisciplinary team of pediatricians, geneticists, orthopedists and hematologists to monitor condition. Genetic counseling of the parents for future pregnancies is also necessary, as well as regular antenatal examinations.

Keywords: thrombocytopenia, absent radius, microdeletion 1q21.1

INTRODUCTION

Thrombocytopenia absent radius (TAR) syndrome is a rare congenital disorder. It presents at birth with low levels of platelets in the blood (thrombocytopenia) and bilateral radius aplasia with the presence of the thumb. The condition of thrombocytopenia and absent radii was first described in 1929 [1] followed by several publications on Hauser in 1948 [2], Bernhard et al in 1951[3], Gross et al in 1956 [4], and Shaw and Oliver in 1959 [5]. As a syndrome TAR was define by Hall et al in 1969 [6].

The frequency of TAR syndrome is about 0.42 cases per 100,000 live births [7] with slight female predominance [8].

TAR syndrome is inherited in an autosomal recessive pattern, but it has been deciphered to follow a more complex pattern [9]. It is the result of noncoding single nucleotide polymorphisms located in the 5′UTR region or the first intron of the gene RBM8A and microdeletion of chromosome 1q21.1 region [10]. In TAR syndrome cases, 75% of the microdeletion is inherited from one parent, and 25% of microdeletions occur de novo. In cases where the carrier status of both parents is known, there is a

25% recurrence risk in each pregnancy for a child with TAR syndrome as in autosomal recessive disorders. In de novo microdeletions, the risk would be approximately 1:100,000 [8].

Skeletal, cardiac, gastro-intestinal, genitourinary anomalies and hematologic disorders are often affected with TAR syndrome.

Diagnosis of TAR syndrome is primarily clinical, based on the presence of thrombocytopenia and characteristic phenotypic features.

In this article we present a case of newborn with bilateral agenesis of the radius and thrombocytopenia.

CASE REPORT

A female late preterm newborn was born in 35 week of gestation from the first uneventful pregnancy of juvenile mother. In the perinatal history there is no data on drug abuse, radiation exposure or consanguinity with the partner. Baby was born by cesarean section with a birth weight of 2,550 grams height 47cm APGAR 6/7 in the first and the fifth minute respectively. After primary resuscitation with T-resuscitator was admitted to Neonatal Intensive Care Unit. It was initiated with O2 mask, antibiotic empiric therapy, anthemorrhagic and antimycotic prophylaxis.

On the first physical examination was noted facial dysmorphia- saddle nose, short nasal bridge, micrognathia, enophthalmus, low-set ears, very short neck, slopping shoulders, hemangioma at the level of the nose and forehead (Figure 1 and 2). Also baby had short limbs, short forearm, radius not palpable, ulnar deviation of the hand and flexion of the legs at the knees, pedes equinovari (Figure 3 and 4).

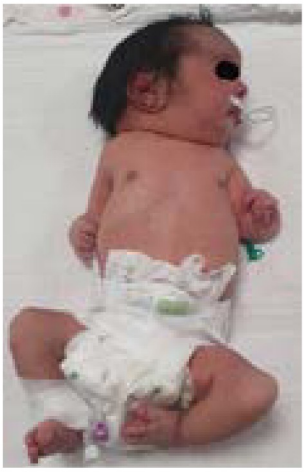

Figure 1 and 2. Facial dysmorphia in newborn with TAR Sy

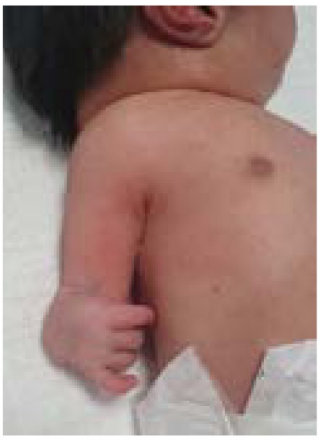

Figure 3. Short forearm, ulnar deviation

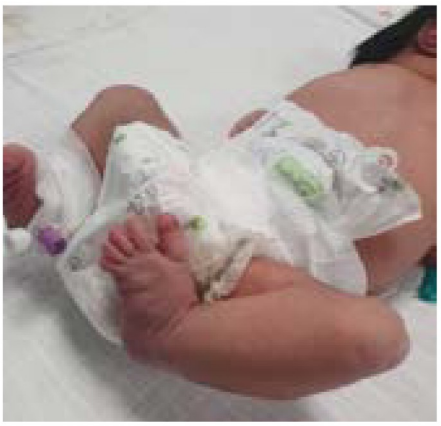

Figure 4. Pedes equinovari

Plain X-ray of both upper limbs reveals bilateral absent radii, shortening and bowing of the ulna, abnormal flexion and radial deviation of both hands (Figure 5).

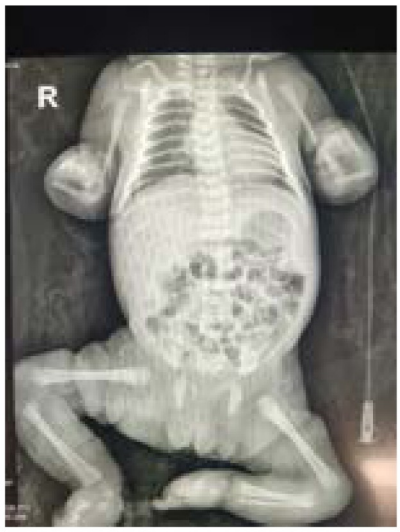

Figure 5. Plane X-ray both upper limbs showing absence of radius and ulnar deviation of the hand

Abdominal and urinary tract ultrasound revealed normal abdominal organs. Heart ultrasound proofed foramen ovale apetum and myocardial hypertrophy. Head ultrasound was normal.

Initial complete blood count (CBC) revealed thrombocytopenia (39x10 9/L). In the next few days was done several CBCs. All of them were with thrombocytopenia (40 x10 9/L, 32 x10 9/L, 56 x10 9/L). Blood culture was sterile. C-reactive protein was in normal range. There were no clinical sings of bleeding.

A newborn receive several platelet transfusion and red blood cell transfusion.

Array genetic testing showed interstitial microdeletion in 1q21.1 in gen RBM8A which confirmed our provisional diagnosis of TAR syndrome.

DISCUSSION

TAR syndrome is rare condition. The incidence of TAR syndrome is approximately 1 in 240,000 births [11].

Skeletal findings on upper and lower limbs are characteristic for TAR syndrome. The upper extremities are more severely affected than the lower extremities, but both groups of extremities can be affected with varying degrees of severity [12]. In addition to bilateral aplasia of the radius the thumbs are hypoplastic and appear flat, wide and held in flexion across the palm and typically their function is abnormal [13]. Lower limb anomalies include hip dysplasia, small patellae with subluxation, positional anomalies of the foot, with significant bowing of the legs [12, 14]. In our case there were skeletal anomalies in upper and lower limbs, short forearm, ulnar deviation of the hand and flexion of the legs at the knees, pedes equinovari.

Cases of TAR have low numbers of megakaryocytes, the precursor cells of platelets in the bone marrow, and present clinically with bleeding episodes in the first year of life [6,15]. The cause of thrombocytopenia is still unclear, several theories have been reported that point to the failure of humoral or cellular producers in megakaryopoiesis. Some studies have suggested that there is a lack of response to thrombopoietin in the signal transduction pathway [1]. The severity of hemorrhagic symptoms is directly correlated with the degree of thrombocytopenia. Clinically, in neonates, they may present with multiple petechial hemorrhages, purpura, hemoptysis, hematuria, hematemesis, and gastrointestinal bleeding [6,16] Intracranial hemorrhage may result in mental retardation or death [17]. An important feature of TAR syndrome is that platelet counts may improve with age, and bleeding decreases [6]. In presented newborn there was thrombocytopenia in all period of hospitalization, with need for platelet transfusion, but without hemorrhagic symptoms.

TAR syndrome may be associated with other non-skeletal abnormalities on gastrointestinal tract and cow's milk intolerance (47%), renal malformations (23%), cardiac defects (15%), facial dysmorphism (53%), short stature (95%), macrocephaly (76%), and capillary hemangioma (24%) [12]. In our case with TAR syndrome there were detected facial dysmorphism, short stature, capillary facial hemangioma and heart defects-foramen ovale apetum and myocardial hypertrophy.

In addition to the clinical presentation of the phenotypic characteristics of patients with TAR syndrome, definitive diagnosis is made by genetic testing. Diagnostic genetic testing for TAR syndrome became available in 2012 when the complete molecular mechanism was deciphered [18]. The most accurate method for detecting TAR syndrome is molecular genetic testing of the RBM8A gene, typically using a combination of (1) Sanger sequencing to detect the causative SNPs and (2) a microdeletion detection method. To identify the exact size of the microdeletion on chromosome 1q21.1, which usually extends beyond the RBM8A gene, molecular karyotyping or other genome-wide methods are useful for detecting copy number variants [8]. We conform our case with array genetic testing which show interstitial microdeletion in 1q21.1.

TAR syndrome illustrates the challenge of interpreting rare and large copy number variants. The genetic heterogeneity underlying TAR syndrome is limited, but in addition to the three core features of TAR, a wide range of additional phenotypes can be observed. One theory posits that variation in gene expression, which can be further modified by environmental factors and statistical chance, explains the variability in TAR-associated phenotypes [10].

Differential diagnosis this genetic condition should be distinguished from Holt-Oram syndrome, Fanconi anemia, Roberts syndrome, Rapadilino syndrome, Thalidomide embriopathy [19].

Therapeutic management of this disorder is directed at the hematologic and skeletal manifestations. Treatment of thrombocytopenia is usually platelet transfusion, although care should be taken not to repeat transfusions too frequently as alloimmunization or rarely infection may result [20,21]. Splenectomy, corticosteroids, and androgens are not effective in patients with TAR syndrome [21]. Treatment of skeletal anomalies is individualized and includes orthopedic surgery, prosthesis, orthotic, and adaptive devices [22].

Genetic counseling and testing of parents should be performed in families where TAR syndrome occurs.

A series of controls should be carried out during pregnancy. Modern prenatal screenings should detect phenotypic and genetic characteristics of suspected fetuses with TAR syndrome.

CONCLUSION

TAR syndrome is a rare condition firstly clinically suspected in neonatal period. Bilateral absence of radius with the presence of the thumb and thrombocytopenia with or without other congenital malformations are the main criteria for the diagnosis of TAR syndrome Patients with TAR syndrome require a multidisciplinary team of pediatricians, geneticists, orthopedists and hematologists to monitor the condition. Genetic counseling of parents for future pregnancies is also necessary, as well as regular antenatal examinations. Our intention in publishing the case report is that health professionals will be able to use this information to effectively treat those diagnosed with TAR in the future.

REFERENCES

1. Ballmaier M, Schulze H, Strauss G, et al. Thrombopoietin in patients with congenital thrombocytopenia and absent radii: elevated serum levels, normal receptor expression, but defective reactivity to thrombopoietin. Blood 1997; 90(2): 612–619.
2. Hauser F. Uber hereditare und symptomatische congenital thromboper. Paediatrics (Basel) 1948; 171:86–91.
3. Bernhard WG, Gore I, Kilby RA. Congenital leukemia. Blood 1951; 6(11):990–1001.
4. Gross H, Groh C, Weippl G. Kongenitale hypoplastische thrombopenie mit radius-aplasia, ein syndrome multipler abartungen. Neue Osterr Z Kinderheilkd 1956; 1:574–582.
5. Shaw S, Oliver RA. Congenital hypoplastic thrombocytopenia with skeletal deformaties in siblings. Blood 1959; 14(4): 374–377.
6. Hall JG, Levin J, Kuhn JP, Ottenheimer EJ, van Berkum KA, McKusick VA. Thrombocytopenia with absent radius (TAR). Medicine (Baltimore) 1969; 48(6):411–439.
7. Cowan J, Parikh T, Waghela R, Mora R. Thrombocytopenia with Absent Radii (TAR) Syndrome Without Significant Thrombocytopenia. Cureus. 2020; 12(9):e10557.
8. Strauss G, Mott K, Klopocki E, Schulze H. Thrombocytopenia Absent Radius (TAR)-Syndrome: From Current Genetics to Patient Self-Empowerment. Hamostaseologie. 2023; 43(4):252-260.
9. Klopocki E, Schulze H, Strauss G, et al. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet 2007; 80(02):232–240
10. Albers CA, Newbury-Ecob R, Ouwehand WH, Ghevaert C. New insights into the genetic basis of TAR (thrombocytopenia-absent radii) syndrome. Curr Opin Genet Dev. 2013; 23(3):316–323.
11. Martinez-Frias ML, Bermejo Sanchez E, Garcia Garcia A, Perez Fernandez JL, Cucalon Manzanos F, Calvo Aguilar MJ, Ripalda Crespo MJ: An epidemiological study of the thrombocytopenia with radial aplasia syndrome (TAR) in Spain. An Esp Pediatr 1998; 49:619-623.
12. Greenhalgh KL, Howell RT, Bottani A, et al. Thrombocytopenia-absent radius syndrome: a clinical genetic study. J Med Genet. 2002; 39(12): 876–881.
13. Goldfarb CA, Wustrack R, Pratt JA, Mender A, Manske PR. Thumb function and appearance in thrombocyto-

penia: absent radius syndrome. J Hand Surg Am 2007; 32(2): 157–161.

14. Christensen CP, Ferguson RL. Lower extremity deformities associated with thrombocytopenia and absent radius syndrome. Clin Orthop Relat Res 2000; 375(375):202–206.
15. Hedberg VA, Lipton JM: Thrombocytopenia with absent radii. A review of 100 cases. Am J Pediatr Hematol Oncol 1988, 10:51-64.
16. Gounder DS, Pullon HW, Ockelford PA, Nicol RO. Clinical manifestations of the thrombocytopenia and absent radii (TAR) syndrome. Aust N Z J Med 1989; 19:479-82.
17. Hall JG. Thrombocytopenia and absent radius (TAR) syndrome. J Med Genet 1987; 24:79-83.
18. Albers CA, Paul DS, Schulze H, et al. Compound inheritance of a low-frequency regulatory SNP and a rare null mutation in exonjunction complex subunit RBM8A causes TAR syndrome. Nat Genet 2012; 44(04):435–439, S1–S2.
19. Toriello HV. Thrombocytopenia-absent radius syndrome. Semin Thromb Hemost. 2011; 37(6):707-12.
20. Geddis AE. Inherited thrombocytopenia: congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radii. Semin Hematol 2006; 43(3):196–203.
21. Aquino VM, Mustafa MM, Vaickus L, Wooley R, Buchanan GR. Recombinant interleukin-6 in the treatment of congenital thrombocytopenia associated with absent radii. J Pediatr Hematol Oncol 1998; 20(5):474–476.
22. Idahosa C, Berardi TR, Shkolnikov R, Stoopler ET. Thrombocytopenia absent radius (TAR) syndrome: a case report and review for oral health care providers. Spec Care Dentist. 2014; 34(5):251-8.