



Severe Extremity Anomaly and Neurodevelopmental Retardation in an Infant with TAR Syndrome and Differential Diagnosis in Radial Defects

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ABSTRACT

Thrombocytopenia-absent radius (TAR) syndrome is a rare congenital syndrome in which thrombocytopenia and the absence of radius can be accompanied by various organ anomalies. Bilateral phocomelia is the most severe form in this clinic. Thumbs are always present. The deletion of the *RNA-binding motif protein 8A (RBM8A)* gene on chromosome 1q21.1 in Array Comparative Genomic Hybridization confirms the diagnosis of TAR syndrome. Thrombocytopenia, which can cause complications, tends to resolve in the first year of life. Although there are delays in motor development, mental retardation is not one of the common clinical findings of this syndrome. In the differential diagnosis of severe radial defects, TAR syndrome, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia, and VACTERL association are included. The presence of key findings of each syndrome is important in the differential diagnosis. Here, we aimed to evaluate the approach to the differential diagnosis of severe radial anomalies in a patient with TAR syndrome and neuromotor retardation.

Keywords: Phocomelia, TAR syndrome, RBM8A, 1q21.1

Introduction

Thrombocytopenia-absent radius (TAR) syndrome (OMIM 274000) is a rare congenital disorder with an estimated prevalence of 1 in 100,000 to 1 in 200,000 births. The cardinal manifestation of TAR syndrome was described by Hall et al. (1) in 1969. It is characterized by thrombocytopenia and bilateral absence of the radii with preservation of both thumbs. However, many additional features, including other skeletal anomalies, heart defects, genitourinary system anomalies, and cow milk intolerance have been reported (2).

Phocomelia, which is defined as the absence of the radius, ulna and humerus and affect function, constitute the most

a severe form of the clinic. Depending on the extent of the upper extremity function, delays in motor developmental stages may be seen in patients, but neuromotor retardation is not a typical finding of this syndrome. In the differential diagnosis of severe radial defects, which can also be detected by fetal ultrasonography (US) in the prenatal period, TAR syndrome, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia and the VACTERL association are included. Finding the key differential findings of each syndrome is important in diagnosis. In this report, we aimed to report on a female infant with TAR syndrome accompanied with severe upper limb phocomelia with neurodevelopmental retardation and to discuss the differential diagnosis of radial anomalies.

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Case Presentation

A 16-day-old female with bilateral upper limb phocomelia was referred to our Pediatric Genetics Department. The patient was the first child of non-consanguineous parents. Family history was normal. The mother was a non-smoker with no history of exposure to teratogenic agents. Routine US performed at 13 weeks of gestation showed bilateral absence of the arm and forearm with both hands being normal. The parent refused to do amniocentesis for fetal karyotyping. She was born at 39 weeks of gestation via cesarean section with APGAR score of 9/10 at 1 and 5 minutes, respectively. At birth, a weight of 2,750 g (-1.32 SDS), a length of 48 cm (-0.66 SDS) and an occipitofrontal head circumference of 34 cm (-0.36 SDS) were measured. Physical examination revealed bilateral upper limb phocomelia with no thumb deformity, radial club hand, splenomegaly, micrognathia, low-set ear, and 5th finger clinodactyly (Figure 1). No abnormality of the lower extremities was noted except for a placement anomaly on the 4th toes of the feet. Laboratory values included a white blood cell measurement of (WBC) $42 \times 10^9/L$, hemoglobin of 9 g/dL, and a platelet count of $11 \times 10^9/L$. Peripheral blood smear showed increased myelocytic activity, thrombocytopenia, and neutrophilia.



Figure 1. Proband showing bilateral absence of the arm and forearm, arm/shoulder muscle hypoplasia with both hands normal, no thumb deformity, low-set ears, and micrognathia

Bone marrow aspiration biopsy was normocellular with undetected megakaryocytes. Additionally, there was no malignant infiltration. Immunological parameters revealed low levels of immunoglobulins and cow milk intolerance. Skeletal X-ray imaging confirmed the bilateral absence of humeri, radii, ulnae, and clavicles with hook like appearance. There was no vertebra or costal anomalies (Figure 2). Transthoracic echocardiography revealed a small ventricular septal defect (VSD). There was no clinical evidence of renal abnormality on the abdominal US. A normal female karyotype (46, XX) was found on chromosomal analysis. On array-CGH, a pathogenic interstitial heterozygous deletion of 562 kb on chromosome 1q21.1 including the *RNA binding motif protein 8A (RBM8A)* was detected.

Bilateral strabismus was noticed at the age of 6 months and she had an operation due to strabismus. An examination at the 20th month revealed that she was unable to sit or walk unassisted. When the psychometric analysis was performed, retardation was observed in motor, adaptive, cognitive, and language development. Cranial MR imaging was normal. At her last examination, her body weight was measured as 7.6 kg (-2.6 SDS), her height was 65 cm (-5 SDS), and her head circumference was 43 cm (-3.1 SDS). She is under follow-up for intermittent screening for thrombocytopenia and her last platelet count was $137 \times 10^9/L$.

Discussion

TAR syndrome is a rare genetic disorder associated with thrombocytopenia and bilateral absence of radii. It



Figure 2. Anteroposterior chest image showing bilateral absence of radius, ulna, and humerus, clavicles with hook-like appearance, no vertebral and costal anomalies

has also been found to be associated with genitourinary malformations (duplicated ureter, horseshoe kidney, renal dysgenesis, agenesis of the uterus, cervix, and the upper part of the vagina), cardiac anomalies (mainly septal defects), dysmorphic features (tall forehead, small chin, low-set ears), and often cow's milk intolerance (2,3). All patients with TAR syndrome have a bilateral absence of the radii, and the thumbs are always present even if they are hypoplastic. The severity of radial anomalies varies from hypoplasia of the radius to phocomelia. In a study including 30 patients, phocomelia was present in 33% of all cases (4). Greenhalgh et al. (2) and Houeijeh et al. (5) found the rate of phocomelia to be 28% and 11%, respectively in their case series with TAR syndrome. Lower limb malformations are often observed, which include hip dysplasia, knee abnormalities, and shortening of the long bones (4). However, upper limb abnormalities tend to be more severe. Our patient had phocomelia, which is the most severe form of upper extremity abnormalities. No major lower extremity abnormality was seen in our case.

The genetic inheritance pattern of TAR syndrome is uncertain, however, a study by Klopocki et al. (4) identified a minimal common interstitial microdeletion of 200-kb on chromosome 1q21.1. This microdeletion in the long (q) arm of chromosome 1 usually involves the deletion of a gene called the *RBM8A* gene. In several cases, it is inherited from an unaffected parent, while in others, it originates de novo and the presence of a 1q21.1 microdeletion is necessary but not sufficient to cause this phenotype. In our study, we could not determine genetic inheritance as the parents declined to undergo genetic testing. Prenatal diagnosis of TAR syndrome is also feasible (6). Radial abnormality can be detected in the early weeks of gestation by the fetal US. The confirmation via molecular genetic testing to detect the deletion in the 1q21.1 allows for the prenatal diagnosis of TAR syndrome.

The exact pathophysiology of thrombocytopenia is still unclear in TAR syndrome. The supposed reason for the low platelet count is the paucity of megakaryocytes. In the first months of life, patients may have severe thrombocytopenia ($<30 \times 10^9/L$), complications such as bleeding, petechiae, and associated mortality may be high (7). The main concern for patients with TAR syndrome is the risk of life-threatening bleeding, however, thrombocytopenia of unknown cause in the neonatal period typically resolves in the first year of life (7). It can also fluctuate over time. Thus, serial platelet count monitoring has been recommended. Our case had petechiae in the neonatal period and received a platelet

transfusion due to her low platelet count. No complications secondary to thrombocytopenia were observed in her clinic, and platelet values started to increase from the third month in line with the literature.

Motor developmental delay can be seen in cases with TAR syndrome due to skeletal system anomalies. However, there are a few studies that report that mental retardation may be present in 7% of patients due to intracranial hemorrhages secondary to thrombocytopenia and that central nervous system pathologies (cerebral, cerebellar anomalies, vascular malformations, epilepsy, etc.) maybe associated with this condition (8-10). There is a study showing that the *RBM8A* gene has a critical role in the regulation of cortical progenitor cells and neurodevelopment (11). The neurodevelopmental retardation of our patient despite her normal MR imaging can be explained by the loss of the regulatory role of the *RBM8A* gene, which is deleted in TAR syndrome, in brain development.

In a study consisting of 20 cases diagnosed with 1q21.1 microdeletion syndrome, 55% had eye anomalies (congenital cataract, strabismus, coloboma, hyperopia, Duane anomaly), and strabismus was observed in 20% of these cases (12). There is little literature on ocular manifestations of TAR syndrome. As an interesting finding, a newborn case in which TAR syndrome was accompanied by bilateral congenital cataracts was reported (13). Our patient had a history of surgery when she was 6 months old due to bilateral strabismus. For this reason, it is important to evaluate the eye examination in detail and to make an early diagnosis of this syndrome. We also hope to contribute to the literature due to the severe strabismus in our case.

TAR syndrome needs to be differentiated from other syndromes which contain radial anomalies such as thalidomide embryopathy, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia, and VACTERL associations. The possible diseases in the differential diagnosis of TAR syndrome are summarized in Table I. The questioning of any possible drug use in the mother's pregnancy can be used to exclude thalidomide embryopathy. Holt-Oram syndrome is associated with upper limb malformations with cardiac abnormalities (atrial septal defect and VSD) (14). Abnormalities of the metacarpals and carpal bones can be seen and the thumbs are usually absent or severely hypoplastic. Roberts syndrome is characterized by severe growth retardation, limb defects, and craniofacial anomalies, and patients may occasionally exhibit normal thumbs (15). Fanconi anemia is caused by a defect in DNA repair, bone marrow suppression, thumb and/or radial

Table I. Differential diagnosis of severe radial anomalies

Condition	Inheritance pattern	Genetic impairment	Upper limb abnormality	Hematologic disorder	Other clinical features
TAR syndrome	AR*	Microdeletion on chromosome 1q21.1	Bilateral absence of the radii with the presence of both thumbs	Hypo-megakaryocytic thrombocytopenia	Lower limb malformations, cardiac anomalies, genitourinary malformations, dysmorphic features, cow's milk intolerance
Holt-Oram syndrome	AD*	Mutation in TBX5	Thumb anomalies most common and the thumbs are usually absent or malformed.	None	Congenital cardiac defects
Roberts syndrome	AR	Mutation in ESCO2	Symmetric reduction in the number of digits, and length or presence of bones. (Thumb aplasia or hypoplasia, phocomelia, oligodactyly, radial, ulnar and humeral aplasia, tetraphocomelia)	None	Craniofacial anomalies, pre- and postnatal growth retardation
Fanconi anemia	AD, AR, X-linked	Defect in DNA repair, different genes can cause	Thumb and/or radial hypoplasia	Bone marrow suppression, pancytopenia and a high risk of developing acute myeloid leukemia	Skin pigmentation, short stature, gastrointestinal tract and genitourinary abnormalities
VACTERL association Vertebral Anal Cardiac Tracheoesophageal fistula/ Esophageal atresia Renal anomalies Limb anomalies	Isolated	Sporadic	Thumb and/or radial hypoplasia/aplasia, radioulnar synostosis, polydactyly, syndactyly Triphalangeal thumb presence	None	Growth deficiency Spinal and cranial abnormalities

*AD: Autosomal dominant, *AR: Autosomal recessive

deformities, and a predisposition to cancer is often present (16). In VACTERL association, the diagnosis is considered in the presence of at least three of the vertebral, anal, cardiac, renal anomalies, and tracheoesophageal fistula/esophageal atresia. Thumb aplasia/hypoplasia, radius anomalies, polydactyly, syndactyly, and lower extremity anomalies can also be seen with varying severity (17). In our patient, the key points that distinguish TAR syndrome from the other syndromes are radial abnormalities and the presence of both thumbs. Additionally, thrombocytopenia is mandatory to differentiate TAR syndrome from other diagnoses. Nevertheless, genetic tests should be used to confirm the clinical diagnosis.

Conclusion

TAR syndrome is a rare syndrome characterized by bilateral absence of the radii with the presence of both thumbs and thrombocytopenia. Clinical features together

with the detection of the 1q21.1 deletion allow clinicians to conclude from the aforementioned differential diagnoses that TAR syndrome is most likely. The risk of bleeding is high during the first year of life. Thrombocytopenia is generally fluctuant in nature, but it is usually transient. Serial monitoring of the platelet count is essential in the management of patients. Patients can have many additional abnormalities, including skeletal, urogenital, and heart defects. Cranial Imaging is recommended in cases with neuromotor retardation. Therefore, patients with TAR syndrome should be assessed for other associated malformations. Orthopedic interventions may be needed to maximize limb function.

Ethics

Informed Consent: Permission was obtained from the patient's parents to share their medical information.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.K., N.Ö., B.N., G.Ü.K., E.M., Design: G.K., B.N., Literature Search: G.K., N.Ö., B.N., G.Ü.K., E.M., Writing: G.K. B.N. E.M.

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