# TAR Syndrome, a Rare Case Report with Cleft Lip/Palate

A Naseh, A Hafizi, F Malek, H Mozdarani, V Yassaee

#### Citation

A Naseh, A Hafizi, F Malek, H Mozdarani, V Yassaee. *TAR Syndrome, a Rare Case Report with Cleft Lip/Palate*. The Internet Journal of Pediatrics and Neonatology. 2012 Volume 14 Number 1.

#### Abstract

TAR (Thrombocytopenia-Absent Radius) is a clinically –defined syndrome characterized by hypomegakarocytic thrombocytopenia and bilateral absence of radius in the presence of both thumbs. *We describe a female neonate as a rare case of TAR syndrome with orofacial cleft. Bone marrow aspiration of the patient revealed a cellular marrow with marked reduction of megakaryocytes. Our clinical observation is consistent with TAR syndrome. However, other syndromes with cleft lip/palate and radial aplasia like Roberts syndrome (tetraphocomelia), Edwards syndrome and Fanconi and sc phocomelia (which has less degree of limb reduction) should be considered. Our cytogenetic study excludes other overlapping chromosomal syndromes. <i>RBM8A analysis may reveal nucleotide alteration, leading to definite diagnosis. Our objective is adding this cleft lip and cleft palate to the literature regarding TAR syndrome. - Eva Klopocki, Harald Schulz, Gabriele Straub, Judith Hall, Fabienne Trotier, et al(February 2007) ;Complex inheritance pattern Resembeling Autosomal Recessive Inheritance Involving a Microdeletion in Thrombocytopenia-Absent Radius Syndrome. The American Journal of Human Genetics 80:232-240* 

# INTRODUCTION

TAR is a clinically-defined syndrome characterized by thrombocytopenia and bilateral radial bone aplasia in the forearm with thumbs present. At birth, thrombocytopenia may be of variable severity with platelet counts ranging from 10-100000/nl usually less than  $50000_{1}$ . Bone marrow examination typically demonstrates a reduction in the size and number of bone marrow megakaryocytes. The platelet count tends to rise as the child gets older. Other skeletal and non-skeletal abnormalities such as phocomelia, cow's milk intolerance, facial dysmorphism and cardiac defects are common. It has been suggested that the reason of the link between skeletal, hematologic and cardiac abnormalities is related to the simultaneous development of the heart, the radii and the megakaryocytes around the gestation age of 6-8 weeks 2. Despite significant interest, the molecular basis of TAR syndrome is really uncertain and autosomal recessive, dominant, and complex pattern can be observed 3. The overall incidence of disease is about 0.5-1/100000 in live born neonates. The main problem for patients with TAR syndrome is hemorrhage due to thrombocytopenia 4. It is hypothesized that TAR syndrome is associated with a deletion on chromosome 1q21.1 but it develops only in the presence of an additional as yet- unknown modifier (mTAR). 5 6

Hemorrhage is the major cause of mortality in TAR

syndrome. The hemorrhage happens during the first 14 months of life. Hedberg and associates concluded in a study that 18 of 20 deaths in 76 patients were due to hemorrhagic incidents; most of patients who died had platelet counts < 10 X  $10^{9}$ /L. <sup>8</sup>

Heart, kidney, lactose intolerance, thumb hypoplasia and knee-joint problem may be seen in the patients.

During the first week of life, purpura, petechiae, epistaxis, melaena, haemoptysis, haematuria, haematemesis and ecchymosis are not uncommon. Intracranial hemorrhage, cerebellar hypoplasia, brachycephaly, squint and ptosis are commonly seen. <sup>9</sup>

Although the molecular basis of TAR syndrome has been undiscovered for several decades, more recently researchers using advanced genomic technology identified a defective gene (ENSG00000131795) called RNA binding motif protein 8A (RBM8A) in TAR patients who also carried the deletion in chromosome 1. This gene controls the production of the protein named Y14. They realized that co-inheritance of a deletion in one copy of chromosome 1 and one normal allele of the RBM8A gene and the variants on the other copy greatly reduces the level of Y14. They concluded that it is low levels of Y14 that affect platelet formation and may result in creation of most TAR patients. Molecular analysis of RMB8a gene can provide definitive diagnosis for existence of TAR syndrome.

# CASE PRESENTATION

A female term neonate with bilateral upper limb malformation, orofacial cleft and respiratory distress was referred to our in-patient clinic. She was the first child of relatively healthy parents who were first cousins. The family history did not show other such cases existing in the family although we cannot confirm or reject the incidence of any stillbirth or miscarriage in the related family. Her mother was 31 years old with one abortion due to unknown reason during the previous year and the history of hypothyroidism which was under treatment with levothyroxine. No prenatal testing had been done. The delivery of the baby was through normal delivery. Physical examination of the neonate revealed bilateral upper limb malformation plus cleft lip and palate. No lower limb abnormality was observed. Birth body weight was 2280 gr and head circumference was 34 cm. She had mild respiratory distress with grunting at the time of admission which improved after 12 hours. In overall, she was stable and became full fed within 3-4 days of admission. Feeding was done through orogastric tube. The X-Ray graphy of her both upper limbs revealed bilateral absence of radius which was confirmed with orthopedic consultation. Other diagnostic imaging such as brain and abdominal ultrasonography was normal although echocardiography showed mild PDA. Several blood cell counts were consistent with thrombocytopenia in contrast with her mother's CBC which was normal. The platelet count was at first more than 50,000 but gradually decreased to less than 25,000. Other chemical laboratory test results such as biochemistry, arterial blood gas, serum lactate and pyruvate, TORCH study (Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes) and thyroid function test (this test is routinely done during the second week of birth in ill patients in our department) were normal.

Patient went under bone marrow aspiration which revealed a cellular marrow with marked reduction of megakaryocytes. The bone marrow cell differentiation was myeloid/erythroid with the ratio of 3/1. When feeding was started, she got diarrhea and abdominal distention probably due to lactose intolerance, so we changed her milk but there was no improvement. Later on, she developed episodes of GI bleeding as the result of severe thrombocytopenia. This resulted in platelet transfusion. The triggering reason for GI bleeding might have been infection. She developed leucopenia, neutropenia, rise in CRP and septic shock.

The patient had a small chin (micrognathia), small upturned nose, wide-set eyes (hypertelorism), low-set posteriorly rotated ears and naevus flammeus on her forehead and she would easily get bruised.

## Figure 1

Figure 1: Bone marrow with reduction of megakaryocytes



# **Figure 2** Figure 2: TAR with cleft lip and palate



# CYTOGENETIC STUDY

For chromosomal analysis, heparinized venous blood was cultured in RPMI-1640 medium supplemented with 10% fetal calf serum and antibiotics (penicillin (100 iu/ml/ Streptomycin 100 µg/ml). 0.1 ml of Phytohemaglutinin (PHA) was added to the culture medium as mitogen to stimulate lymphocyte division. Harvesting and slide preparation was done using standard method. Slides were stained in DAPI fluorescent stain (Fig. 3A) and analyzed under a fluorescent microscope to check for premature centromere division (PCD), also with Giemsa stain (Fig. 3B) to check numerical chromosome abnormalities. As seen in figure 3 A and B, the chromosome complement shows 46 chromosomes with no premature centromere division (PCD). This observation exclude trisomy 18 (Edward's syndrome)<sup>10</sup> and Robert's syndrome<sup>11</sup>. PCD is cytogenetic characteristics of Robert's syndrome. However, we are aware that fluorescent in situ hybridization (FISH) analysis is possible for detection of such microdeletions. However, since the clinical observations and the exclusion of other overlapping chromosomal syndromes are all in favor of TAR syndrome, the need for further chromosomal verification of this case is minimal.

#### Figure 3

Figure 3. (A) Photomicrograph of metaphase chromosomes stained in DAPI shown as inverted DAPI picture (Magnification x1000); and (B) Metaphase chromosomes stained in Giemsa (Magnification x1000).



## DIFFERENTIAL DIAGNOSIS

Roberts syndrome is a genetic (autosomal recessive) disorder with limb and facial abnormalities. Slow pace of growth of the fetus continues after birth. There is 50% chance of intellectual impairment. <sup>12</sup>

All four limbs show abnormalities. Arm and leg bones are short (hypomelia), particularly the bones in their forearms and lower legs. If the limbs are so short that the hands and feet are located very close to the body it is called phocomelia. Abnormal or missing fingers and toes are common in Roberts syndrome. Arms are usually more severely affected than legs.

Facial abnormalities, including an opening in the lip (a cleft lip) with or without an opening in the roof of the mouth (cleft palate), a small chin (micrognathia), ear abnormalities, wide-set eyes (hypertelorism), outer corners of the eyes that point downward (down-slanting palpebral fissures), small nostrils, and a beaked nose are seen. They may have a small head size (microcephaly), and in severe cases affected individuals have a sac-like protrusion of the brain (encephalocele) at the front of their head. In addition, people with Roberts syndrome may have heart, kidney, and genital abnormalities. Mutations in the ESCO2 gene cause Roberts syndrome. Roberts syndrome is cytogenetically characterized by premature centromere division (PCD).

# (EDWARDS' SYNDROME)

Edwards' syndrome is trisomy 18, with an extra chromosome 18 instead of the usual pair. It is a severe disorder that can affect all organs in the body. Features that may be noted after birth include: Low birth weight and craniofacial abnormalities (low-set and malformed ears, micrognathia (small jaw), prominent occiput., small facial features, e.g. microphthalmia, microstomia, microcephaly, cleft lip and palate and/or narrow palate and coloboma of iris).<sup>13</sup>

Fanconi syndrome is a nephrotic-glucosuric dwarfism with hypophosphatemic rickets, and amino acids in the urine. The problem is in the proximal segment of the renal tubule. The genetic defects which decrease the ability of body to metabolize some molecules such as cystine, fructose, galactose and glycogen cause the accumulation of these molecules in the body and damage the kidneys. <sup>14</sup>

Acidosis, calciuria, and phosphaturia, affect bone accretion and thus, reduce growth. Some forms of Fanconi syndrome, such as cystinosis, lead to renal failure.

Fanconi syndrome is usually inherited in an autosomal recessive pattern.

The clinical picture includes cataracts (accumulation of cystine in cornea which is pathognomonic), splenomegaly, and hepatomegaly (can lead to cirrhosis),

hyperaminoaciduria, albuminuria, and galactosuria and/or glucosuria.  $^{\rm 15}$ 

Pierre Robin Sequence or Complex is a birth condition involving either a small (micrognathia) or set back (retrognathia) lower jaw resulting in the displacement of the tongue towards the throat and causing the obstruction of the airway. Cleft palate (without cleft lip) is common.<sup>16</sup>

# DISCUSSION

TAR syndrome with the combination of cleft palate and lip is extremely rare. Hence, respiratory and feeding problems should be taken into consideration for the patients' care. Although the main presentative indexes in TAR syndrome are absence of radius and thrombocytopenia, additional skeletal abnormalities are frequently observed including more extensive upper limb malformations, phocomelia and lower limb malformations in as many as 47% of the patients. Non skeletal abnormalities are also common including gastroenteritis and cow's milk intolerance in 47%, renal malformations in 23%, cardiac defects in 15%, facial dysmorphism in 53%, short stature in 95 % and macrocephaly in 76% of the patients. The researchers have found that the colony-forming unit (CFU)-MK number was decreased by blood or marrow CD34+ cells.<sup>17</sup>

Treatment includes platelet transfusions and sometimes surgery in order to correct the appearance of the shortclubbed arm. The infant mortality rate has been curbed by new technology, including platelet transfusions, which can even be done inside uterus. The first year of life is the critical period since in most people with TAR, platelet counts improve as they grow out of childhood.

In TAR syndrome, thumbs are present, which are missing in other types of malformations involving an absent radius. Short stature and additional skeletal abnormalities, including underdevelopment of other bones in the arms and legs are seen. Malformations of the heart and kidneys are common. This disorder is associated with unusual facial features including a small lower jaw (micrognathia), a prominent forehead, and low-set ears. Galactose intolerance (cow milk) is common.

In all the cases diagnosed with TAR syndrome, a deletion of about 200,000 DNA building- blocks from the long (q) arm of chromosome 1 at position 1q21.1 has been seen. <sup>18</sup> This section of chromosome 1 contains 11 genes. The loss of multiple genes in this region is believed to be responsible for the signs and symptoms of TAR syndrome.

Researchers believe that in addition to the 1q21.1 200 kb deletion, some other, unknown genetic change to cause TAR syndrome must also be present.

TAR syndrome's inheritance pattern is unclear. The deletions on chromosome 1 at position 1q21.1 can be passed through generations in families. Affected individuals usually have the deletion in only one copy of chromosome 1. Since an additional genetic change is also believed to be involved in this disorder, the inheritance pattern is complex.

Not all people who inherit the chromosome 1 deletion associated with TAR syndrome will develop the disorder. Also, deletions can happen during early development in people with no family history.

Severe bleeding which may occur in the brain and other organs usually is the cause of death in the first year of age. Children, who survive this period without any damaging bleeding in the brain, usually have a normal life expectancy and intellectual development.

### Figure 4

Figures 4and 5: Lack of Radius bone in forearm in TAR



# TAR SYNDROME IN CONCLUSION

Since TAR syndrome follows probably an autosomal recessive inheritance pattern, when a child has this condition, there is 25% chance that the future siblings will be affected. Hence, genetic counseling for parents and considering the option of termination of the pregnancy should be discussed.

At the time of delivery, Cesarean section should be considered to minimize the trauma to a neonate with low platelet count.<sup>19</sup>

Genetic counseling for the future pregnancies is advised. Hence, either pregnancy can be terminated or intrauterine platelet transfusion to save the baby can be administered. Fetal ultrasonography to detect malformations and also, cordocentesis to detect deletion in chromosome 1 and also acquiring fetal peripheral blood smear to identify hypomegakaryocytosis can be recommended.

Future studies to further clarify the differential diagnostic criteria for the syndromes involving radial aplasia and cleft lip/palate are needed.

There is no documented statistics for the prevalence of TAR syndrome in Iran (however, three cases have been reported by Ansari and Vosoogh). <sup>20</sup> Therefore, additional studies as well as participation in national or international organizations may be helpful in gaining more information. In our country, we need more rehabilitative centers which are specialized for these kinds of patients and their special needs.

#### References

1. Eva Klopocki, Harald Schulz, Gabriele Straub, Judith Hall, Fabienne Trotier, et al (February 2007) ;Complex inheritance pattern Resembeling Autosomal Recessive Inheritance Involving a Microdeletion in Thrombocytopenia-Absent Radius Syndrome. The American Journal of Human Genetics 80:232-240

2. Pagon RA, Bird TD,Dolan CR,et al(1993), Thrombocytopenia Absent Radius Syndrome. GeneReviews .Seattle(WA):University of Washington, Seattle,NBK23758 3-3-3 -

PMDI:20301781http://emedicine.medscape.com/article/959 262-overview#a0104 3.

4. K L Greenhalgh, R T Howell, A Bottani, P J Ancliff, H G Brunner, et al(2002), Thrombocytopenia-Absent radius syndrome:a clinical genetic study J Med Genet 39:876-881 5. Ipek Akil, Salih Gozmen, Omer Yilmaz, Can Taneli(2008), Kidney stone and urinary bladder telangiectasia in a patient with TAR syndrome. The Turkish Journal of Pediatrics 50:509-511 6. Eva Klopocki(2007), Thrombocytopenia; Research data from Charite University update understanding of thrombocytopenia.Cardiovascular Week.Atlanta:pg 203 7. Eva Klopocki, Harald Schulze, Gabriele straub, Claus-Eric Ott, et al, Complex Inheritance pattern Resembling Autosomal Recessive Inheritance Involving a Microdeletion in Thrombocytopenia-Absent Radius Syndrome. American Journal of Human Genetics 80:Iss. 2;pg 232 8. Hedberg VA, Lipton JM. Thrombocytopenia with absent radii. A review of 100 cases. Am J Pediatr Hematol Oncol. Spring 1988;10(1):51-64. [Medline].

http://emedicine.medscape.com/article/959262-clinical#a021 7

10. Pont SJ, Robbins JM, Bird TM, Gibson JB, Cleves MA, Tilford JM, Aitken ME (2006) Congenital malformations among liveborn infants with trisomies 18 and 13. Am J Med Genet ;140 (16): 1749-56.

11. K. Madan, D. Lindhout and A. Palan (1987) Premature centromere division (PCD): a dominantly inherited cytogenetic anomaly . Human Genetics, 77 (2) , 193-196. 12. Hou F, Zou H. Two human orthologues of Ecol/Ctf7 acetyltransferases are both required for proper sister-

chromatid cohesion. Mol Biol Cell, 2005, Aug. 16(8): 3908-18.

13. Leask K; Edwards Syndrome, National Library for Health, Genetic Conditions Specialist Library, July 2005 14. Seifter JL. Potassium disorders. In: Goldman L, Ausiello D, eds. Cecil Medicine. 23rd ed. Philadelphia, Pa: Saunders Elsevier; 2007:chap 118.

15. Kapitsinou PP, Ansari N. Acute renal failure in an AIDS patient on tenofovir: a case report. J Med Case Reports. Mar 31 2008;2:94.

16. Cohen, MM Jr. (1999). Robin Sequence and Complexes. American Journal of Medical Genetics 84: 311-315.

17. Letestu, R(2000), TAR Syndrome; Thrombocytopenia Associated with Dysmegakaryocytopoiesis.Blood

Weekly.Atlanta:pg 20

18. Bonsi L, Marchionni C, Alviano F, Lanzoni G, Franchina M, Costa R, Grossi A, Bagnara GP. Thrombocytopenia with absent radii (TAR) syndrome: from hemopoietic progenitor to mesenchymal stromal cell disease? Exp Hematol. 2009 Jan;37(1):1-7.

19. Ballmaier M, Schulze H, Strau G, et al. Thrombopoietin in patients with congenital thrombocytopenia and absent radii: elevated serum levels, normal receptor expression, but defective reactivity to thrombopoietin. Blood, Vol. 90 No. 2 (July 15), 1997: pp. 612-619. J Am Soc Hematol. 20. Ansari SH., Vossogh P., Three Cases of

Thrombocytopenia-Absent Radii (TAR) Syndrome in Ali-Asghar Children's Hospital (2005) 12, vol 47.

## **Author Information**

Ali Naseh, MD Dept. of Pediatrics, Shahid-Beheshti University of Medical Sciences

Ali Hafizi, MD Dept. of Pediatrics, Shahid-Beheshti University of Medical Sciences

### Fatemeh Malek, MD

Dept. of Pediatrics, Shahid-Beheshti University of Medical Sciences

Hossein Mozdarani, Ph.D Dept. of Medical Genetics, Faculty of Medical Sciences, Tarbiat-Modares University

Vahid R. Yassaee, MD-PhD Genomic Research Center, Shahid-Beheshti University of Medical Sciences