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Tar- Syndrome – (Thrombocytopenia - Absent Radius Syndrome)

KEYWORDS: Thrombocytopenia, autosomal recessive disorder, micro deletion

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ABSTRACT *Back ground: Thrombocytopenia-absent radius syndrome (TAR) is a rare autosomal recessive disorder combining specific skeletal abnormalities with a reduced platelet count.*

Material & method: A 3day old male baby born at 35-36 weeks of gestation to a primigravida with non-consanguinous marriage,was brought to Niloufer hospital, in view of preterm with respiratory distress.

Observations &result: In this case report The child is the first male child of apparently healthy nonconsanguineous parents. The mother was 20 years old at the time of his birth. Unilateral radial deviation of the left hand. X-ray confirmed absence of radius along with absence of first metacarpal & skeleton of the thumb in left upper limb. The child alspresented with thrombocytopenia (55,000/cumm), The phenotypic features were characteristic of TAR syndrome. .

Discussion&conclusion: This is a case of Atypical TAR syndrome because unilateral dysplastic radius in association with isolated thrombocytopenia, along with absence of 1st metacarpal and thumb. the identification of the 1q21.1 deletion allows for confirmation of the TAR syndrome diagnosis, particularly in patients with atypical phenotypes, and it also allows for accurate genetic counseling, especially when it occurs de novo.

INTRODUCTION:

Thrombocytopenia with absent radius is a rare genetic disorder that is characterised by the absence of radius bone in the forearm and a dramatically reduced platelet count. Incidence:0.42 per 1,00,000 live birth. It was first identified in 1956. TAR syndrome (Thrombocytopenia -Absent-Radius) syndrome is characterized by thrombocytopenia that may be episodic, congenital skeletal deformities including bilateral absence of radius, shortening and deformity of the ulnae, and occasionally absence of all the long bones in the arm. The fingers and thumbs are always present, while other skeletal anomalies are frequent. But this is a case of Atypical TAR syndrome because unilateral dysplastic radius in association with isolated thrombocytopenia, along with absence of 1st metacarpal and thumb.

MATERIAL &METHOD:

A 3day old male baby born at 35-36 weeks of gestation to a primigravida with non-consanguinous marriage,was brought to Niloufer hospital, in view of preterm and respiratory distress.

antenatal history: -age of mother 20yrs.-G1P1L1; ante-natal checkups-irregular; no history of maternal hypertension, diabetes mellitus, asthma,epilepy. -no history of drug intake. intrapartum history: -hospital delivery.-mode of delivery is LSCS.-indication-? Oligohydramnios; baby cried immediately after birth; no history of PROM, prolonged labor; gestational age 35-36 weeks; family history-non consanguinous marriage. -first in birth order.

OBSERVATIONS AND RESULT:

general examination: -baby warm and pink.capillary refilling time is 3sec; alert;.cry, activity- normal; no umbilical discharge; left fore arm shortening with radial deviation of hand.-absent thumb. -spine normal.-no other external congenital anamolies. Anthropometry: weight 1.8 kg, length 46 cm, head circumference 35cm, Upper segment:Lower segment-1.8:1. Other systems: Cardiovascular system:S1 presents, split in S2. Respiratory system:bilateral air entry present. Central nervous system: no abnormality detected. Neonatal reflexes: asymmetric moros, sucking, rooting reflexes are normal. Investigations: Hb-16gm/dl, TLC-8000/cumm, Platelet count-55000/cum.X-Ray revealed absence of radius and presence of only ulna in left forearm. 2D-echo : 3.5mm ASD with left to right shunt. Ultrasongraphic study of his abdomen and brain were normal. On the basis of clinical presentation, physical findings, isolated thrombocytopenia, and X-ray results, the diagnosis of TAR syndrome with atypical presentation was made. But this is a case of Atypical TAR syndrome because unilateral dysplastic radius in association with isolated thrombocytopenia, along with absence of 1st metacarpal and thumb.

Platelet abnormality reflects platelet hypo production. Lack of response to thrombopoietin. Generally considered as autosomal recessive.Male:Female=1:1.

Treatment range from platelet transfusions to surgery aimed at centralising the hand over the ulna to improve function of the hand. For most people with TAR syndrome, platelet counts improve as they grow out of childhood.

DISCUSSION & CONCLUSION:

TAR syndrome (Thrombocytopenia -Absent-Radius) syndrome is characterized by thrombocytopenia that may be episodic, congenital skeletal deformities including bilateral absence of radius, shortening and deformity of the ulnae, and occasionally absence of all the long bones in the arm. The fingers and thumbs are always present, while other skeletal anomalies are frequent [1]. In this case report The child is the first male child of apparently healthy nonconsanguineous parents. The mother was 20 years old at the time of his birth. Unilateral radial deviation of the left

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hand. X-ray confirmed absence of radius along with absence of first metacarpal & skeleton of the thumb in left upper limb. The child also presented with thrombocytopenia (55,000/cumm), The phenotypic features were characteristic of TAR syndrome. Although we have diagnosed this case as Atypical TAR syndrome, but still there is a big question that, is it Atypical TAR Syndrome or a new syndrome? . Because in this present case there is unilateral absence of radius along with the first metacarpal & skeleton of thumb in left upper limb, the right upper limb was normal.

TAR syndrome is an autosomal recessive inherited disorder characterized by bleeding manifestation due to isolated thrombocytopenia and bilateral absent radius. Thrombocytopenia, which may be transient, but present in 100% of cases diagnosed with TAR syndrome [1]. TAR syndrome without thrombocytopenia does not exist, but the platelet count varies from case to case. In earlier study, researchers found that patients with TAR syndrome are usually diagnosed at birth, due to thrombocytopenia as they present with petechial rash or bleeding manifestation like bloody diarrhea in the first week of life or later during the next four months. Platelet counts at birth are usually 15,000 to 30,000/uL [2,3]. But in the present case platlet count is 55,000/cumm and there is no history of any signs and symptoms of thrombocytopenia like petechial rash or bleeding manifestation like bloody diarrhea. Patient is came to the hospital for respiratory distress.

The exact pathophysiology of the thrombocytopenia is still unclear, but it may be explained by the following different mechanisms: (1) the absence of humoral or cellular stimulators of megakaryocytopoiesis (2), the absence of megakaryocytic progenitor cells (3), cellular defects in megakaryocytic precursors (for example, receptor defects) or (4) the presence of humoral or cellular inhibitors of megakaryocytopoiesis [2]. In our case bone marrow aspiration cytology was not done because parents did not given consent for bone marrow aspiration cytology.

Other characteristic feature of TAR Syndrome is bilateral absence of radii. In contrast to this, our case demonstrated only unilateral dysplasia of radius and radial deviation of the left forearm along with absnce of thumb and 1st metacarpal . Other upper limb anomalies (aplasion and hypoplasion of ulna and humerus, hypoplasion of carpal bones, sindactylia, clinodactylia are rare[4]. None of the lower limb anomalies were present in our case. However, the frequency of appearance of the lower limb anomalies (hips dysplasia, femoral and tibial torsion, pes equinovarus and equinovalgus and knee deformations) may be present in 47% [2]. Congenital heart anomalies (Tetralogy of Fallot, atrial and ventricular septum anomalies) appeared in 22-33 % of the cases [1,2]. In the present case there was an atrial septal defect of 3.5mm with left to right shunt.All changes of limbs and other organs of TAR syndrome that were here described can be present at the syndromes and other diseases (Holt-Oram syndrome, Fanconi anemia, VACTERLS Association, Cornelia de Lange syndrome: embriopathy due to thalidomide etc.), which may be considered with the differential diagnosis with TAR syndrome [5,6].

Megakaryocytes are absent in two thirds of the bone marrows aspirated and the rest are decreased in number and are small, immature and vacuolated[7]. In an attempt to understand the genetic basis of TAR syndrome, Klopocki *et al.* reported that TAR syndrome has a complex pattern of inheritance associated with a common interstitial microdeletion of 200kb on chromosome 1q21.1 and an additional, as yet unknown, modifier[8]. Houeijeh *et al.* mentioned that the identification of the 1q21.1 deletion allows for confirmation of the TAR syndrome diagnosis, particularly in patients with atypical phenotypes, and it also allows for accurate genetic counseling, especially when it occurs *de novo*[9].

The genomic structure of the 1q21.1 breakpoint regions is extremely complex, with at least four large segmental duplication blocks ranging in size from 270kb to 2.2Mb. Within 1q21.1 there are two areas where a deletion can be found: the TAR area for the TAR syndrome and the distal area for other anomalies. The 1q21.1 deletion syndrome will commonly be found in the distal area, but an overlap with the TAR area is possible[10]. A chromosome 1q21.1 microdeletion was identified in 30 patients affected by TAR syndrome [11]. This microdeletion is mediated by Low Copy Repeats (LCRs) that can be at the basis of recurrent DNA rearrangements such as deletions, duplications and inversions through chromosome or chromatid misalignment followed by non-allelic homologous recombination (NAHR) [12-14].

Recently, it has been shown that compound inheritance of a rare null allele and one of the two low-frequency noncoding SNPs (rs139428292 or rs201779890) in *RBM8A* are crucial for TAR syndrome [15]. In fact, a study identified two rare **single nucleotide polymorphisms** (SNPs) in the regulatory region of the *RBM8A* gene that are involved in TAR syndrome through the reduction of the expression of the RBM8A-encoded Y14 protein [15]. Albers et al.[16,17], explained that TAR phenotype could be also influenced from other factors such as environmental factors altering gene expression, incomplete penetrance or additional modifier alleles. It is interesting to note that, among the several genes with a known function located within the region, the *PIAS3* gene could be indicated as the most conspicuous candidate for thrombocytopenia and the *Lix1L* gene, known be transiently expressed during chick hind-limb development, could be proposed as the candidate gene for limb abnormalities [18-20].

In Pregnancies known to be at increased risk for TAR syndrome : prenatal diagnosis can be made by

Molecular genetic testing. If the pathogenic variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers testing for pathogenic variants in *RBM8A* and the 200-kb minimally deleted region at 1q21.1.

Fetal ultrasound examination. Ultrasound evaluation of fetal limbs and heart can be used either alone or in conjunction with molecular genetic testing.

COMPETING INTERESTS: None.

PATIENT CONSENT : Obtained.

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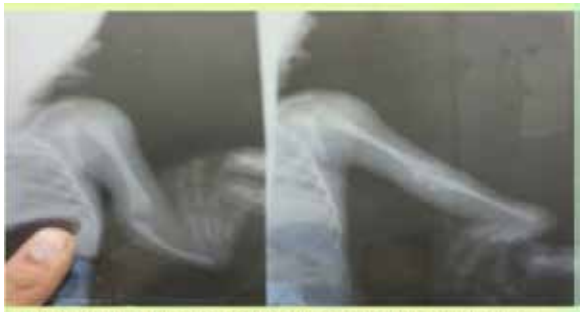

fig-1: X-ray showing absence of radius in forearm with absence of 1st metacarpal & thumb skeleton along with radial deviation of hand .

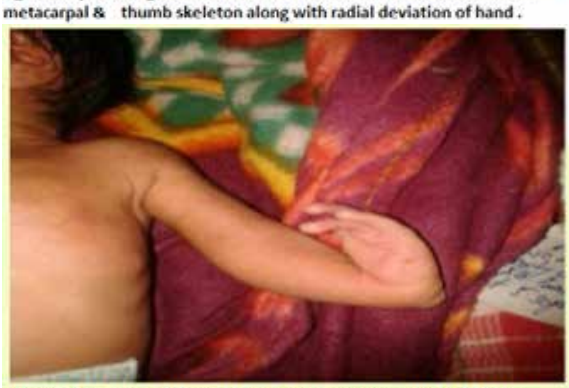

fig-2: showing absence of radius along with radial deviation of hand in left upper limb

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