Thrombocytopenia-Absent Radius Syndrome

Thrombocytopenia-absent radius (TAR) syndrome is a congenital malformation syndrome characterized by bilateral absence of the radii and congenital thrombocytopenia.

GENETICS/BASIC DEFECTS

1. Genetic inheritance: autosomal recessive inheritance, based on the following observations
   a. Families with at least two affected children born to unaffected parents
   b. Rare instances of association with consanguinity
2. Etiology of thrombocytopenia: unknown but is considered to be the result of a decreased production of platelets from the bone marrow

CLINICAL FEATURES

1. Thrombocytopenia (100%)
   a. May be transient
   b. Symptomatic in over 90% of cases within the first four months of life
      i. Purpura
      ii. Petechiae
      iii. Epistaxis
      iv. Gastrointestinal bleeding
         a) Hematemesis
         b) Melena
      v. Hemoptysis
      vi. Hematuria
      vii. Intracerebral bleeding
   c. More severe thrombocytopenia can be precipitated by stress, infection, gastrointestinal disturbances, or surgery
   d. Platelet count tends to rise as the child gets older and may approach normal levels in adulthood (spontaneous improvement of platelet counts after one year)
2. Upper extremity anomalies (100%)
   a. Bilateral absence of the radius (100%): the most striking skeletal manifestation
   b. Hand anomalies
      i. Presence of the thumbs (100%)
         a) An important clinical feature distinguishing TAR syndrome from other disorders featuring radial aplasia, which are usually associated with absent thumbs
         b) Relatively functional thumbs
         c) Thumbs often adducted
         d) Thumbs often hypoplastic
      ii. Radially deviated
      iii. Limited extension of the fingers
      iv. Hypoplasia of the carpal and phalangeal bones
   c. Associated ulnar anomalies
      i. Usually short
      ii. Usually malformed
      iii. Absent ulna
         a) Absent bilaterally in about 20% of cases
         b) Absent unilaterally in about 10% of cases
   d. Associated humeral anomalies
      i. Often abnormal in about 50% of cases
      ii. Absent humeri in about 5–10% of cases (rare phocomelia)
   e. Associated shoulder and arm anomalies
      i. One arm shorter than the other in about 15% of cases
      ii. Hypoplasia of muscles and soft tissue in the arm and shoulder
      iii. Abnormal shoulder joint secondary to abnormal humeral head
3. Lower limb anomalies (47%)
   a. Correlation exists between the severity of skeletal changes in the lower limbs and the severity of abnormalities of the upper limbs
   b. Variable involvement but usually milder than the upper limbs
      i. Dislocation of the patella and/or of the hips
      ii. Knee involvement
         a) Dysplasia: rare severe knee dysplasia due to agenesis of cruciate ligaments and menisci
         b) Ankylosis
         c) Subluxation
      iii. Hip dislocation
      iv. Coxa valga
      v. Absent tibiofibular joint
      vi. Femoral or tibial torsion
      vii. Lower limb phocomelia
      viii. Valgus and varus foot deformities
      ix. Abnormal toe placement
      x. Severe cases with lower limb phocomelia
4. Cow's milk intolerance (62%)
   a. Presentation symptoms
      i. Persistent diarrhea
      ii. Failure to thrive
   b. Thrombocytopenia episodes
      i. Precipitated by introduction of cow's milk
      ii. Relieved by its exclusion from the diet
5. Urogenital anomalies (23%)
   a. Horseshoe kidney
   b. Absent uterus
6. Cardiac anomalies (22–33%)
   a. Tetralogy of Fallot
   b. Atrial septal defect
   c. Ventricular septal defect
7. Other associated congenital anomalies
   a. Facial capillary haemangiomata in the glabella region
   b. Micrognathia
   c. Cleft palate
   d. Intracranial vascular malformation

e. Sensorineural hearing loss
f. Epilepsy
g. Other skeletal anomalies
    i. Scoliosis
    ii. Cervical rib
    iii. Fused cervical spine
    iv. Short stature
h. Neural tube defect

8. Prognosis
    a. Variable clinical course among patients
    b. Survival related to the severity and duration of thrombocytopenia
    c. Good prognosis after surviving the first year of life
    d. Early diagnosis and treatment with platelet therapy minimize mortality risks
    e. Mental retardation secondary to intracranial bleed (7%)
    f. Good hand and upper extremity functions, especially if bilateral radial aplasia is the only skeletal abnormality
9. Differential diagnosis
    a. Holt-Oram syndrome
        i. An autosomal dominant condition caused by mutations in the *TBX5* gene
        ii. Often with a family history of heart and limb defects
        iii. Absence of the thumb associated with radial aplasia
        iv. Absence of thrombocytopenia
    b. Roberts syndrome
        i. An autosomal recessive trait
        ii. Pre- and postnatal growth retardation
        iii. Facial clefting
        iv. Genitourinary abnormalities
        v. Limb defects involving upper or lower limbs or both
        vi. Characteristic chromosome abnormality in the majority (79%) of cases
            a) Premature centromeric separation (PCS)
            b) "Puffing" of the chromosomes caused by repulsion of the heterochromatic regions near the centromeres of chromosomes 1, 9, and 16 with splaying of the short arms of the acrocentric chromosomes and of distal Yp.33
            c) Evidence of abnormal mitosis
        vii. Postulated that TAR syndrome and Roberts syndrome might be part of the same condition with TAR syndrome being the milder and Roberts the severer variants
    c. Fanconi anemia
        i. An autosomal recessive disorder
        ii. Bone marrow failure
        iii. Skeletal defects
        iv. Cutaneous pigmentation
        v. Microcephaly
        vi. Short stature
        vii. May present with thrombocytopenia
        viii. Upper limb abnormalities also involve the radial ray
        ix. Hypoplastic thumbs may be accompanied by radial hypoplasia but absence of the radius is associated with absence of the thumbs
        x. Spontaneous chromosome breakage, a consistent feature of Fanconi anemia and is a reliable diagnostic test
    d. Aase syndrome
        i. Radial hypoplasia
        ii. Triphalangeal thumbs
        iii. Hypoplastic anemia, similar to Blackfan-Diamond syndrome
        iv. Thrombocytopenia not a feature
    e. Thalidomide embryopathy
        i. May present with radial anomalies of the upper limb
        ii. Malformations of the lower limbs showing a less consistent pattern
        iii. Diagnosed based on:
            a) Phenotype
            b) History of exposure to thalidomide during pregnancy
            c) Increasing use of thalidomide as a therapeutic agent for the treatment of conditions such as Beçhet's disease, graft vs host disease, multiple myeloma, and Kaposi's sarcoma
    f. Rapadilino syndrome
        i. Absent thumbs and radial aplasia/hypoplasia
        ii. Patellar aplasia/hypoplasia
        iii. Cleft palate
    g. Other syndromes with limb reduction abnormalities predominantly involving the upper extremities
        i. Adams-Oliver syndrome
            a) Transverse limb defects
            b) Aplasia cutis congenita
            c) Growth deficiency
        ii. Aglossia-adactylia
            a) Absence/hypoplasia of digits
            b) Absence/hypoplasia of the tongue
        iii. Amniotic band sequence
            a) Limb constriction or amputation
            b) Asymmetric facial clefts
            c) Cranial defects
            d) Compression deformities
        iv. CHILD syndrome
            a) Unilateral hypomelia
            b) Ichthyosiform erythroderma
            c) Cardiac septal defect
        v. Cornelia de Lange syndrome
            a) Micromelia
            b) Growth deficiency
            c) Facial dysmorphism
        vi. Femur-fibula-ulnar syndrome
            a) Femoral/fibular defects associated with malformations of the arms
            b) Amelia
            c) Peromelia at the lower end of the humerus
            d) Humeroradial synostosis
            e) Defects of the ulna and ulnar rays
        vii. Poland anomaly
            a) Unilateral defect of pectoralis major muscle
            b) Ipsilateral limb abnormalities
        viii. VATER association (vertebral, anal, tracheoesophageal, renal and radial anomalies)

ix. Weyers ulnar ray/oligodactyly syndrome
a) Deficient ulnar and fibular rays
b) Oligodactyly
c) Hydronephrosis
h. Megakaryocytic aplasia
i. Amegakaryocytic thrombocytopenia
ii. Congenital hypoplastic thrombocytopenia with microcephaly
iii. Thrombocytopenia associated with trisomy 13 and trisomy 18

DIAGNOSTIC INVESTIGATIONS

1. Hematological studies
a. Blood platelet counts: thrombocytopenia
b. Anemia secondary to bleeding
c. Eosinophilia
d. Leukemoid reaction
i. Reported in about 60–70% of patients during the first year of life
ii. White blood counts >35,000 per mm^3 with a shift to the left, particularly with the stress and infections
iii. Usually associated with worse thrombocytopenia and often with hepatosplenomegaly
e. Bone marrow aspirates
i. Normal or hypercellular bone marrow
ii. Hypomegakaryocytic thromobocytopenia (<100,000 platelets per mm^3)
a) Absence of megakaryocytes in two thirds of cases
b) Decreased in number of megakaryocytes, which are small, immature, basophilic, and vacuolated, in the rest of cases
2. Chromosome analysis: normal to differentiate from chromosome abnormality syndrome
3. Radiography
a. Upper extremities
i. Bilateral radial aplasia
ii. Radial club hand
iii. Hypoplastic carpals and phalanges
iv. Thumb and fingers always present
v. Hypoplastic ulnae, humeri, and shoulder girdles
vi. Syndactyly and clinodactyly of fingers and toes
b. Lower extremities
i. Hip dislocation
ii. Femoral torsion
iii. Tibial torsion
iv. Knee dysplasia
v. Absent patella
vi. Valgus and varus foot deformities
vii. Abnormal toe placement
viii. Overriding toes

GENETIC COUNSELING

1. Recurrence risk
a. Patient's sib: 25%
b. Patient's offspring: not increased unless the spouse is a carrier
2. Prenatal diagnosis: reported mostly in pregnancies with a prior affected sibling
a. Ultrasonography
i. Bilateral radial aplasia
ii. Club hands with normal thumbs and metacarpals
b. Cordocentesis to evaluate fetal platelet count (thrombocytopenia) and anemia
3. Management
a. Platelet infusions
i. Remains the only real option for treatment of thrombocytopenia
ii. To prevent the intracerebral hemorrhage, which was previously the main cause of mortality
iii. Potential risks of platelet transfusion
a) Infection (hepatitis viruses, HIV)
b) Anaphylaxis
c) Hemolytic reaction
b. Injury prevention strategies
i. Avoid contact sports
ii. Use appropriate protective gear (helmet, padding)
c. Splenectomy usually effective for the treatment of thrombocytopenia in adults
d. Bone marrow transplantation as an option for patients who continue to remain thrombocytopenic with bleeding despite platelet transfusions
e. Physical and occupational therapies to improve function and quality of life
f. Management of the upper extremity
i. Postpone surgery till later as thrombocytopenic related bleeding problems are less frequent in older individuals
ii. Prosthetic fitting is generally rejected by patients as most patients are able to perform tasks by approximating themselves closely enough to an object to use their own hands.
iii. Adaptive devices for feeding, dressing, and toileting are generally well tolerated.
g. Management of the lower extremity
i. Rejection of any lower extremity intervention by most patients
ii. Use of power wheelchair or motorized cart for ambulation

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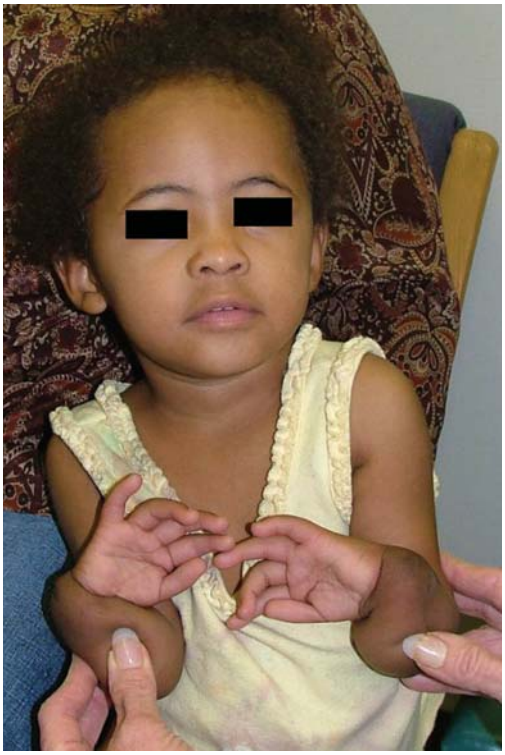


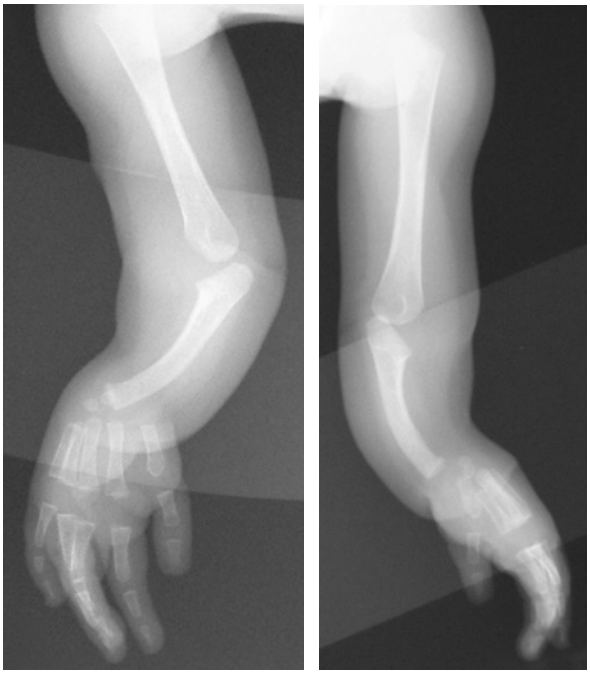
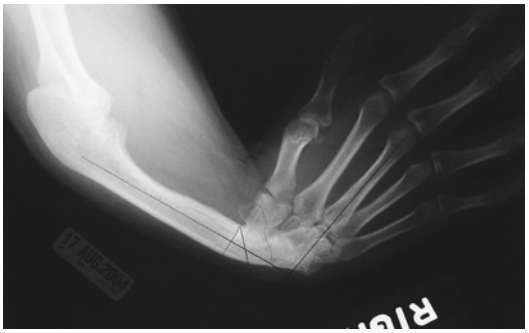


Fig. 1. A 2½ year-old girl with TAR syndrome showing club hands with finger-like thumbs and radial aplasia, illustrated by radiographs. The patient had thrombocytopenia early in life.



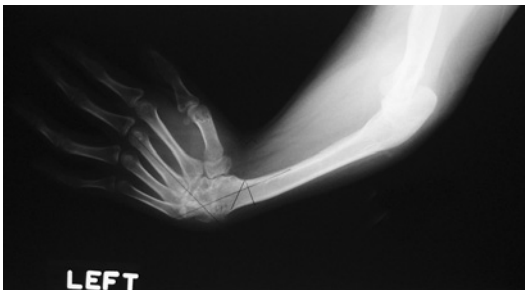


Fig. 2. A 14-year-old boy with TAR syndrome showing similar clinical and radiographic features.