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Thrombocytopenia and absent radius (TAR) syndrome

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Thrombocytopenia and absent radius (TAR) has become recognised as a relatively common congenital anomaly syndrome characterised by hypomegakaryocytic thrombocytopenia (less than 100 000 platelets per mm³) and bilateral absence of the radius with an autosomal recessive pattern of inheritance. Initially the condition was considered to be a form of Fanconi's anaemia; however, by 1969 a total of 40 cases had been reported and it could be distinguished as a specific entity with a quite different natural history from Fanconi's anaemia.¹ Subsequently, more than a hundred cases have been published from all over the world representing a broad spectrum of ethnic groups. A variety of interesting hypotheses has been made, but the pathogenic mechanisms producing the syndrome are still not understood. The clinical features of TAR include haematological abnormalities (of platelets, white cells, and possibly red cells), skeletal abnormalities (primarily of both arms and legs), cardiac abnormalities (particularly tetralogy of Fallot and atrial septal defects), and cow's milk allergy or intolerance (leading to gastrointestinal disturbance in the first few years of life). A number of other unusual features have been described.

Haematological abnormalities

The most striking haematological abnormality is, of course, thrombocytopenia which results from decreased production from megakaryocytes. Thrombocytopenia occurs in almost 100% of patients and is symptomatic in about 90% of patients during the first four months of life.¹ Megakaryocytes from bone marrow aspirations are small, basophilic, and vacuolated. 'Storage pool disease' of platelets has been reported in two cases.^{2,3} Thrombocytopenia is episodic but can be

quite severe in infancy with platelet counts often below 10 000 per mm³. It appears from histories that thrombocytopenia is precipitated by stress, infections, gastrointestinal disturbances, and surgery. Platelet counts are usually in the 15 000 to 30 000 range in infancy and improve to almost normal range by adulthood. Platelet aggregation and survival times are reduced.⁴

Leukaemoid reactions have been recorded in about 60 to 70% of patients during their first year of life.¹ White blood counts greater than 35 000 per mm³ with a shift to the left occur, again particularly with stress and infections. Thrombocytopenia is usually worse during these leukaemoid reactions and hepatosplenomegaly often occurs during them. A few of the cases of TAR from older reports have been described as having leukaemia, but in retrospect these were probably leukaemoid reactions, since true leukaemia has never been documented in a patient with TAR.

Eosinophilia, both in bone marrow and peripheral blood smears, has been seen in about half of the patients with TAR, particularly those who have an allergic response to cow's milk.¹

Anaemia is described in a large number of patients. It is not clear whether this is entirely related to blood loss from bleeding secondary to thrombocytopenia or whether there may be a shortened RBC lifespan. There appears to be a haemolytic component to the anaemia, particularly during the first year of life.

Skeletal abnormalities (figs 1 to 3)

The most striking skeletal abnormality is bilateral absence of the radius which is present in 100% of cases¹ and the diagnosis of TAR should not be considered unless there is complete absence of the radius bilaterally. Necropsy dissection of limbs in TAR syndrome indicates that the radius was never

FIG 1 Note petechiae and short arms with radially deviated hands. Hands have all five fingers.

FIG 2 Note short arms with complete hand. Also note abnormal leg and knee.

present since the muscles which would have attached to the radius are attached instead to the carpal bones.⁵ In contrast to other conditions with absence of the radius, the thumb is always present and relatively functional in TAR.¹ If the thumbs are absent, other diagnoses must be considered. The only other condition in which bilateral absence of the radius and the presence of thumbs has been seen is in some cases of Roberts' syndrome.⁶ The hands in TAR cannot really be considered normal in that there is limited extension of fingers, radial deviation of the hand, and hypoplasia of the carpal and phalangeal bones.

The ulna is abnormal in TAR. It is somewhat shortened and malformed in all cases but is absent bilaterally in about 20% of cases and unilaterally in 10% of cases. The humerus is abnormal in at least half of the cases and absent bilaterally in 5 to 10% of cases. In this situation, the five fingered hand arises from the shoulder.¹ About 15% of cases are asymmetrical in that one arm is much shorter than the other. The shoulder joint may be abnormal

depending on whether or not a normal head of the humerus has been present. Hypoplasia of muscle and soft tissue in the arm and shoulder may also occur. Typically, the hand is radially deviated and becomes more so with age. This probably occurs because of the abnormal attachment of the muscles which usually attach to the radius; they are attached to the lateral carpals and with contraction pull the wrist over radially.⁵

Although not initially described, the legs are involved in about 50% of cases of TAR. Involvement includes dislocation of the hips, subluxation of the knees, coxa valga, dislocation of the patella, femoral and tibial torsion, abnormal tibiofibular joint, ankylosis of the knee, small feet, and various foot deformities with abnormal toe placement (scrambling of the toes).¹ It would appear from the cases which have been described that severity of upper limb involvement correlates with severity of lower limb involvement, that is, the shorter the upper arms, the more likely that the knees and legs will be involved. Even with severe shortening of the

FIG 3 Note totally absent radius with presence of full hand.

lower leg and absence of the fibula, all five toes are present and there is a well formed foot. Three cases of ankylosis of the femur to the residual bone in the lower limb have been described.⁷⁻⁹ In these cases, there may be a right angle between the femur and the lower leg bone. Four cases have been described in which there is only one bone in the leg. From the experience regarding the arm in TAR, one would anticipate that this single bone is the femur, but proper pathological dissections are not yet available. In less severe cases of lower limb involvement in TAR, various types of instability of the knees occur with subluxation of the distal fibula medially and posteriorly behind the femur. Approximately 20% of TAR patients have significant lower limb involvement which manifests as either stiff or subluxing knees.¹

Other skeletal abnormalities in TAR include minor rib and spine abnormalities and hypoplasia of the mandible and maxilla.

Stature

Patients with TAR are short compared with other family members. On average, their height is around the 10th centile of the normal height curve, which means that many patients with TAR are well below the 3rd centile; however, they grow parallel to the 3rd centile. No specific endocrine abnormalities have been found to be responsible for the mild short stature observed.

Cardiac abnormalities

Cardiac abnormalities occur in approximately 30%

of cases of TAR. These are primarily tetralogy of Fallot and atrial septal defects, but one case of dextrocardia has been reported. Congestive heart failure and anaemia in the face of a surgically uncorrected congenital heart anomaly has been the cause of death in some patients in the past. With the availability of platelet transfusion, corrective cardiac surgery should be undertaken if indicated.

Other abnormalities

Other anomalies which have been reported include ptosis,¹⁰ dysseborrhoeic dermatitis leading to bleeding in the skin,¹¹ excessive perspiration, pedal dorsal oedema,¹² lateral clavicular hook,¹³ pancreatic cyst,¹⁴ Meckel's diverticulum, and uterine anomalies.¹ Mental retardation has been reported but it appears in all cases to be related to intracranial bleeding and not due to a basic structural CNS abnormality. Similarly, glaucoma has been reported and, again, this appears to be related to intraocular bleeding.

Natural history

The natural history of TAR during the first few years of life includes a number of problems. Cow's milk allergy or intolerance is relatively common and exposure to cow's milk may precipitate episodes of thrombocytopenia, eosinophilia, and leukaemoid reactions.¹⁵ Diarrhoeal illness with associated thrombocytopenia used to be a common cause of death before platelet transfusions were available. At least three patients have had trials of withdrawal of cow's milk and had exacerbation of haematological

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embryogenesis, since the embryonic blood vessels seem to be the primary gradient in the developing limb around which bone and muscle are formed. It can be postulated that abnormal formation of vessels could then lead to a failure of normal formation of the radius, and in rare cases to failure of normal bones of the lower leg. Because of the abnormal white cell (leukaemoid and eosinophil reaction) responses and the unusual reaction to cow's milk in the first year, there would appear to be some continuing dysfunction of white cells as well as megakaryocytes during the first few years of life. These white blood cell abnormalities are outgrown with age. The thrombocytopenia improves and is usually not a problem for the adult with TAR. Thus, we have a condition which severely affects limb and sometimes heart development during embryogenesis but, in addition, has ongoing effects in postuterine life.

PARENT SUPPORT GROUPS

A parent's support group called TARSA has recently developed for patients with TAR. A parent newsletter and exchange of information about various treatments are available for families who would be interested. Their address is: TARSA, Thrombocytopenia Absent Radius Syndrome Association, 312 Sherwood R D 1, Linwood, New Jersey 08221, USA. Phone: (609) 927-0418.

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