Syndrome of the month

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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 mm^3) 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 mm^3. 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 mm^3 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 cases[1] 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

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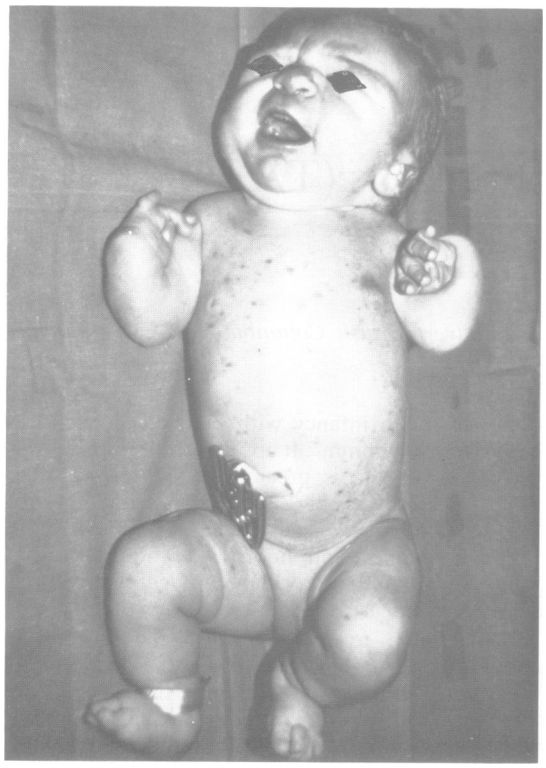

FIG 1 *Note petechiae and short arms with radially deviated hands. Hands have all five fingers.*

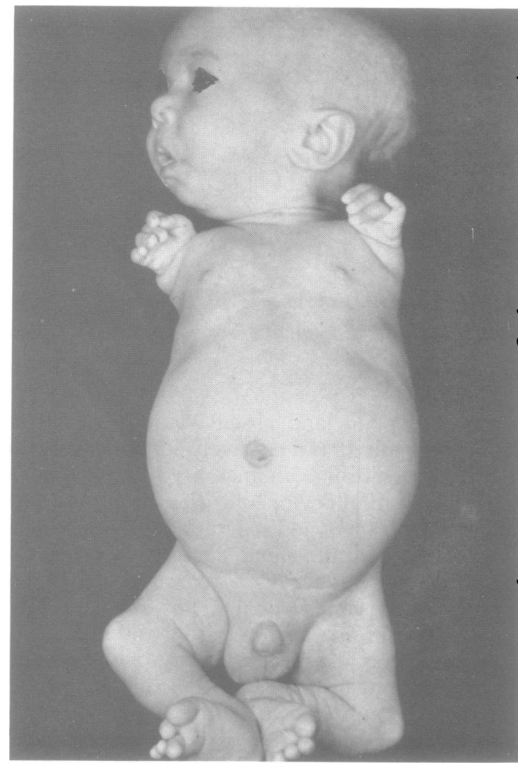

FIG 2 *Note short arms with complete hand. Also note abnormal leg and knee.*

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

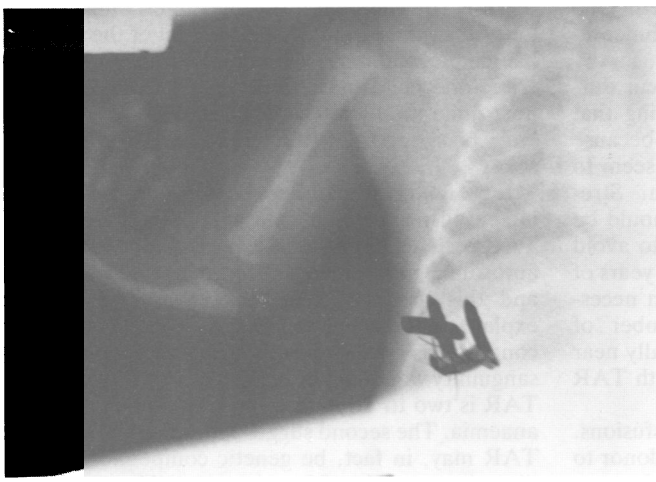

FIG 3 *Note totally absent radius with presence of full hand.*

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

problems when cow's milk was reintroduced. One severely affected patient required hyperalimentation for the first year of life.

Significant symptomatic bleeding may occur during the first two years of life. Infants during that period need to be monitored carefully, because viral, particularly gastrointestinal, illnesses seem to precipitate episodes of thrombocytopenia. Strenuous support for the thrombocytopenia should be provided in the first year. It may be wise to avoid excessive social contacts during the first two years of life to avoid exposure to more viruses than necessary. Gradually over childhood the number of platelets increase and by adulthood are usually near normal levels most of the time. Women with TAR often have menorrhagia.

Many TAR children require platelet transfusions. If possible, they should be given from one donor to try to avoid developing platelet antibodies. Surgery for most orthopaedic problems can be put off until the child is larger and in less danger of severe thrombocytopenia. The only surgery which may be absolutely necessary in the first few years of life would be cardiac surgery and this has been managed in several patients by platelet transfusions.

If severe intracranial bleeding occurs, it is almost always before one year of age and may be associated with later mental retardation.[1] However, delayed motor development is common in TAR because of both the hand and wrist anomalies and the generally short limbs.

Bracing, splinting, or stabilisation of the wrist centrally is often important to keep the hand from deviating radially and to maintain the function of the hand. With severe radial deviation of the wrist, nerve compression and vascular compression can occur. Arthritis of the wrist and knees has occurred in older patients and is thought to be due to the trauma of subluxation in both wrists and knees.

There is no evidence that patients with TAR have a particular susceptibility to viral illness, but five patients from Nigeria have been described as having hypogammaglobulinaemia.[16] This has not been described in patients in North America or the UK. The diarrhoeal illnesses seen in association with cow's milk intolerance during the first year of life in TAR could also have been responsible for loss of protein into the gut in the Nigerian patients.

Inheritance

Thrombocytopenia and absent radius occurs in families in a pattern consistent with autosomal recessive inheritance, that is, parents of a child with thrombocytopenia and absent radius have a 1 in 4 risk of having another affected child.[1] Interestingly, there is considerable intra- and interfamilial variability as to the extent of involvement of the skeletal, haematological, and cardiac anomalies. For instance, one child may be severely affected and the next quite mildly affected. Dizygotic affected twins have been reported.[17] A mild excess of females is seen.

It is of interest that there does not appear to be an increased incidence of consanguinity in families of TAR patients. One would expect in a relatively rare autosomal recessive condition to see consanguinity, and this has not been observed.[1] Two possible explanations have been put forward. Firstly, the condition is not rare and therefore frequent consanguinity would not be expected. In our experience, TAR is two to three times as common as Fanconi's anaemia. The second suggestion is that patients with TAR may, in fact, be genetic compounds, that is, like a haemoglobin SC patient; possibly one allele is for a disorder like Fanconi's anaemia and the other for one like Roberts' syndrome. There is no evidence to support this suggestion as yet. However, there is a very interesting report from Turkey of a child with TAR whose father appeared to have an abnormality consistent with Fanconi's anaemia.[18] In addition, there is a report of a child with many features of TAR who only had unilateral absence of the radius.[15] This report may represent a variant, a heterozygote of TAR, or a peripheral 'back' mutation from a homozygous to heterozygous state in the normal arm. One instance of parent to child pseudodominant transmission of TAR has been observed in a non-consanguineous family which may also imply that the gene is relatively common.

Because of the observed 25% recurrence risk, families should be offered prenatal diagnosis, which can be accomplished with ultrasound[19] by measurement of long bones and determining the presence or absence of the radius, but has also been reported using fetoscopy[17] and *x* rays.[20] In those families electing to continue the pregnancy, caesarian section should be considered for the affected child in order to avoid the trauma of vaginal delivery and the possible role that stress may have on further decreasing platelets. The prognosis for an affected child with TAR appears to be quite good if the child survives the first year with a normal life span after the first two years of life.

The mechanism during embryogenesis leading to this multiple congenital anomaly syndrome is not clear. Interestingly, the primordial megakaryocyte seems to play some role in blood vessel formation and may also play a role in formation of the heart and normal closure of the septum. In addition, the primordial megakaryocyte may play a role in normal vascular bifurcation in the developing limb during

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 oesinophil 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.

References

1. Hall JG, Levin J, Kuhn JP, *et al.* Thrombocytopenia with absent radius (TAR). *Medicine* 1969;**48**:411–39.
2. Day HJ, Holmsen H. Platelet adenine nucleotide "storage pool deficiency" in thrombocytopenic absent radii syndrome. *JAMA* 1972;**221**:1053–4.
3. Zahavi J, Gale R, Kakkar VV. Storage pool disease of platelets in an infant with thrombocytopenic absent radii (TAR) syndrome simulating Fanconi's anaemia. *Haemostasis* 1981;**10**:121–33.
4. Sultan Y, Scrobohaci ML, Rendu F. Abnormal platelet function, population, and survival-time in a boy with congenital absent radii and thrombocytopenia. *Lancet* 1972;**ii**:653.
5. Stephens TD. Muscle abnormalities associated with radial aplasia. *Teratology* 1983;**27**:1–6.
6. Grosse FR, Pandel C, Wiedemann HR. The tetraphocomelia-cleft palate syndrome. *Humangenetik* 1975;**28**:353–6.
7. Anyane-Yeboa K, Jaramillo S, Nagel C, Grebin B. Tetraphocomelia in the syndrome of thrombocytopenia with absent radii (TAR syndrome). *Am J Med Genet* 1985;**20**:571–6.
8. Pfeiffer RA, Maintz G. Tetraphocomelia and neonatal amegakaryocytic thrombocytopenia. *Humangenetik* 1973;**17**:175–8.
9. Ray R, Zorn E, Kelly T, *et al.* Lower limb anomalies in the thrombocytopenia absent radius (TAR) syndrome. *Am J Med Genet* 1980;**7**:523–8.
10. Leclerc J, Toth J. Thrombocytopenia with absent radii. *Can Med Assoc J* 1982;**126**:506–8.
11. Boranic M, Raic F, Puretic S, Zergollern L. Skin disorder in an infant with congenital thrombocytopenia and aplasia of the radial bones. *Acta Med Iugosl* 1979;**33**:67–74.
12. Feingold M, Bartoshesky L, Geis N. Syndrome of the month. *Am J Dis Child* 1980;**134**:895–6.
13. Ingual M, Giedion A. The lateral clavicle hook: its objective measurement and its diagnostic value in Holt-Oram syndrome, diastrophic dwarfism, thrombocytopenia absent radius syndrome and trisomy 8. *Ann Radiol* 1979;**22**:136–41.
14. Juif JF, Stoll C, Korn R.Thrombopenie hypoplasique congenitale avec aplasie du radius. *Arch Fr Pediatr* 1972;**29**:513–26.
15. Whitfield MF, Barr DGD. Cow's milk allergy in the syndrome of thrombocytopenia with absent radius. *Arch Dis Child* 1976;**51**:337–43.
16. Adeyokunnu AA. Radial aplasia and amegakaryocytic thrombocytopenia (TAR syndrome) among Nigerian children. *Am J Dis Child* 1984;**138**:346–8.
17. Filkins K, Russo J, Bilinki I, *et al.* Prenatal diagnosis of thrombocytopenia absent radius syndrome using ultrasound and fetoscopy. *Prenat Diag* 1984;**4**:139–42.
18. Altay C, Sevgi Y, Pirnar T. Fanconi's anemia in offspring of patient with congenital radial and carpal hypoplasia. *N Engl J Med* 1975;**293**:151–2.
19. Luthy DA, Hall JG, Graham CB. Prenatal diagnosis of thrombocytopenia with absent radius. *Clin Genet* 1979;**15**:495–9.
20. Omenn GS, Figley MM, Graham CB, Heinrichs WL. Prospects for radiographic intrauterine diagnosis—the syndrome of thrombocytopenia with absent radii. *N Engl J Med* 1973;**288**:777–8.

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