

Anaesthesia recommendations for patients suffering from

Thrombocytopenia- Absent Radius (TAR) syndrome

Disease name: Thrombocytopenia- Absent Radius (TAR) syndrome

ICD 10: Q87.2

Synonyms: Absent radii and thrombocytopenia, Thrombocytopenia absent radii, Thrombocytopenia absent radius syndrome, Radial Aplasia Amegakaryocytic Thrombocytopenia, Radial Aplasia Thrombocytopenia Syndrome, Radial Aplasia-Amegakaryocytic Thrombocytopenia, TAR Syndrome.

Thrombocytopenia- absent radius syndrome is an uncommon congenital malformation condition characterized by bilateral absence of the radii with the presence of thumbs, and congenital thrombocytopenia. The syndrome is phenotypically variable. It is inherited in an autosomal recessive pattern caused by a 200kb deletion including or null mutation of RBM8A on one chromosome and a non-coding polymorphism in RBM8A on the other chromosome. The estimated prevalence is between 0.5- 1:100,000 and 1:240, 000 births. It affects both sexes equally. Over 150 cases have been previously reported.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

The combination of thrombocytopenia and absent radii was first described by Greenwald and Sherman in 1929, and delineated as a syndrome with a description of cardinal manifestations by Hall et al in 1969 [1,2].

The most common clinical features are:

Thrombocytopenia (100%) - symptomatic in over 90% of the cases within the first four months of life. Platelet counts are usually in the range of $15 - 30 \times 10^9/L$ in infancy and improve to almost normal range by adulthood. The thrombocytopenia is thought to be secondary to impaired bone marrow production of platelets, despite normal thrombopoietin production and slightly elevated serum levels. The number of megakaryocytes in the bone marrow is strongly reduced. Platelet aggregation and survival times are reduced but overall platelet function tends to be normal and bleeding occurs secondary to low platelet numbers [3,4].

Purpura, petechiae, epistaxis, gastrointestinal bleeding, hemoptysis and hematuria are the usual symptoms. Intracerebral bleeding may also occur but is rare. Severe thrombocytopenia can be precipitated by stress, infection, gastrointestinal disturbances, pregnancy and surgery.

The risk of bleeding may be more severe than expected from the platelet count. Some clinicians suggest that advanced coagulation tests including thromboelastography and platelet function analysis may be of additional benefit before major surgery. The main cause of mortality is hemorrhage [5].

Upper extremity anomalies (100%): Unilateral or bilateral absence of the radius, hand anomalies (presence of thumbs, limited extension of the fingers, hypoplasia of the carpal and phalangeal bones, ulnar, humeral and shoulder anomalies [4].

Lower limb anomalies (47%- 62%): Hip and patellar dislocation, knee dysplasia or ankylosis, phocomelia, valgus and varus foot deformities [4].

Cow's milk intolerance: Thrombocytopenia may be precipitated by drinking of cow's milk and relieved by its exclusion from the diet [4,6].

Urogenital anomalies (6-23%): Absent uterus and horseshoe kidney [4,6].

Cardiac anomalies (22-33%): Tetralogy of Fallot, ASD, VSD [1].

Other associated congenital anomalies: Micrognathia, cleft palate, intracranial vascular malformation and facial capillary haemangioma in the glabellar region, epilepsy, scoliosis [6].

The differential diagnosis of TAR syndrome includes:

Fanconi anaemia, Roberts syndrome, Holt-Oram syndrome, thalidomide embryopathy, Cornelia de Lange syndrome, VACTERL association, CHILD syndrome, Trisomy 13 and 18, and Rapadilino syndrome.

Typical surgery

Treatment of the musculoskeletal abnormalities includes orthopaedic reconstructive surgery with subsequent orthotic and prosthetic fitting, dental and orthodontic surgery, cardiac surgery, splenectomy, caesarean section, cardiac catheterization, maxillofacial surgery and plastic surgery. Hand surgery in specialized centres.

Type of anaesthesia

Regional anaesthesia may be contraindicated depending on the severity of the thrombocytopenia . Peripheral nerve or neuroaxial blocks, if performed should take into account coagulation status and the potential risks and benefits of the technique. A safe platelet count has not been established in this syndrome but a platelet count greater than $80 \times 10^9/L$ is recommended for an epidural catheter insertion and removal [7].

The platelet count of at least $80 \times 10^9/L$ should be achieved before performing spinal anaesthesia [7].

Fisher et al reported 9 cases in 4 patients with TAR syndrome who had successful axillary brachial plexus block for perioperative analgesia and anaesthesia [8].

Case reports have been published describing anaesthetic management of patients with TAR syndrome who had orthopaedic procedures, caesarean section, cardiac operations and/or laparoscopic surgery under general anaesthesia [8,9,10,11].

Necessary additional diagnostic procedures (preoperative)

To assess the severity of the disease in an individual diagnosed with thrombocytopenia absent radius (TAR) syndrome, the following evaluations are recommended:

Genetic analysis (Presences of SNPs and microdeletions or mutations in RBM8A. In the presence of thumb aplasia, Fancini anaemia should be excluded through chromosomal breakage analysis.

- Platelet number and function. Values however may not fully reflect bleeding risk.
- The anatomic findings of both upper and lower limbs may lead to extreme difficulties with vascular access and limited sites for invasive and non-invasive blood pressure monitoring. Non-invasive monitoring should be used where possible.
- ECG and Echocardiography to establish the presence or the extent of any cardiac abnormalities
- Evaluation of renal structure and kidney function relevant to anaesthesia [13].

Particular preparation for airway management

Comprehensive airway assessment is essential, especially if micrognathia and cleft palate are present, and a detailed plan for airway management should be established.

Particular preparation for transfusion or administration of blood products

As thrombocytopenia is the main clinical feature, platelet transfusion is the mainstay of the therapy. The platelets are available either as:

Random donor platelets – usually available as pheresis units, one adult therapeutic dose (ATD) is equivalent to four to six single donor units. In children the dose is 10– 15 ml/kg [7].

Or:

HLA- selected platelets (as pheresis units) – product of choice for all patients with TAR syndrome [7].

The patients with TAR syndrome may require blood transfusion during highly invasive surgery and significant blood loss.

Tranexamic acid and Desmopressin (DDAVP) have been used therapeutically to prevent or manage bleeding related to thrombocytopenia [7].

Recombinant activated factor VII has been successfully used as an alternative approach to reduce significant blood loss in planned surgery [17].

There are a small number of cases describing administration of recombinant erythropoietin and recombinant interleukin [6] to induce an increase in platelet count for elective surgery in patients with TAR syndrome [14,15]. Although, not studied in this patient group to date, eltrombopag and romiplostim may be the therapeutic options to increase platelet count. Consultation with a hematologist is strongly advised before considering these therapies.

Bone marrow transplantation has been reported as a choice of treatment in a patient with TAR syndrome with persistent thrombocytopenia and hemorrhagic complications [18].

Particular preparation for anticoagulation

There are no specific recommendations for anticoagulation in patients with TAR syndrome.

For the patients at risk of thrombosis, the use of anticoagulants should be weighed against the risk of bleeding in thrombocytopenia on an individual basis. The risk of thromboembolic disease in TAR syndrome has not been determined. In paediatrics, increased risk exists in those with prior DVT/PE, prolonged intensive care unit stay and those with central lines, particularly at the femoral site [21].

Mechanical prophylaxis (compression stockings, pneumatic devices and early immobilisation) should also be considered.

For therapeutic dose, anticoagulation in patients with severe thrombocytopenia the Anglo-American cancer guidelines on anticoagulation in cancer patients recommends:

Anticoagulation is not administered, no matter what the platelet account is, in patients with life-threatening bleeding or bleeding requiring transfusion (WHO grade III/IV). Consider a vena cava filter in DVT patients [15]. In all other patients (no bleeding, petechiae, hematomas, stable Hb (WHO grade 0/I/II) consider anticoagulation [15]. In patients with platelets counts $\geq 50 \times 10^9/L$, start standard dose anticoagulation [15]. With lower counts $< 50 \times 10^9/L$, give half standard dose and increase to full dose when platelets are $\geq 50 \times 10^9/L$ [15].

Particular precautions for positioning, transport or mobilisation

The patients with TAR syndrome are typically short, with multiple musculoskeletal abnormalities, have undergone numerous surgeries and have some orthopaedic adaptive devices in place. Meticulous attention to protect pressure points and the limbs during the transport and positioning on the operating table is needed.

Probable interaction between anaesthetic agents and patient's long-term medication

No drug interactions have been described.

Avoid NSAID's and Aspirin (possible exacerbation of platelet dysfunction).

Anaesthesiologic procedure

Patients with TAR syndrome are considered as high anaesthetic risk patients and should be assessed in preoperative assessment clinic or by experienced consultants prior to their surgery.

Multiple venous cannulations prior to the surgery and anatomic abnormalities may result in extreme difficulties with venous and arterial access. Ultrasound guidance may be useful for vascular access [9].

Micrognathia is present in over 50 % of patients and may be associated with difficult intubation [5].

Particular or additional monitoring

Placement of the blood pressure cuff may be challenging or impossible. Femoral or brachial access should be considered as alternatives for Invasive monitoring.

Tunneled or peripherally inserted central lines may be beneficial for multiple surgeries requiring administration of blood products and blood sampling perioperatively [9,18].

Possible complications

Due to the presence of cardiac disease there may be an increase in the risk of paradoxical embolism.

Higher risk of blood -born diseases and alloimmunization due to frequent transfusion.

Bleeding from the surgical site, central and arterial lines, the throat and the trachea (LMA and ETT) and neuraxial blocks attributable to the thrombocytopenia.

Postoperative care

High dependy unit/Intermediate care is recommended for 24 hours with very close attention to the coagulation status.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

Thrombocytopenia may be exacerbated by intercurrent illness, particularly infection.

Ambulatory anaesthesia

Suitability for day case depends on the severity of the disease and the surgical procedure.

Obstetrical anaesthesia

Thrombocytopenia may be exacerbated during pregnancy.

The main considerations in peripartum care are the impact of thrombocytopenia on feasibility of neuraxial blockade, surgical bleeding and difficult vascular access.

A detailed strategy should be made in advance between the haematologist, obstetrician and anaesthetist.

A safe level of platelet count for performing neuraxial block has not been established. Neither neuraxial anaesthesia nor analgesia has been described for patients with TAR syndrome to date.

Remifentanyl PCA for analgesia in labour and multimodal approach with opioid PCA for analgesia post caesarean section are alternative strategies.

Anaesthetic management of a parturient with TAR syndrome for cesarean section has been reported by Lynch and al and has been complicated by marked thrombocytopenia and difficult vascular access [9].

Another case of anaesthetic management of a primigravida with TAR syndrome and thrombocytopenia aggravated at her late pregnancy successfully treated with steroids has been described by Bot-Robin et al [19].

Assessment of coagulopathy in a patient with TAR syndrome undergoing caesarean section using TEG has been reported by Gauthama et al but remains unvalidated [16].

Wax et al have reported maternal thrombocytopenia-absent radius syndrome complicated by severe pre-eclampsia and highlighted the importance of advanced planning for vascular access, choice of anaesthetic technique and collaboration with local blood bank [20].

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Please note that this guideline has not been reviewed by an anaesthesiologist but by two disease experts instead.
