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Case Reports

Spastic Diplegia as a Complication of Interferon Alpha Treatment of Kasabach-Merritt Syndrome

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Abstract Treatment of life threatening and yet steroid non-responsive Kasabath-Merritt syndrome patient with interferon alpha during infancy is associated with potentially irreversible spastic diplegia. Physicians should balance the risk and benefit of interferon treatment. Repeated clinical assessment of neuro-developmental status is mandatory in those interferon treated infants. Early discontinuation of interferon alpha treatment has the potential of reversal of early onset spastic diplegia.

Key words Interferon alpha; Kasabach-Merritt Syndrome; Spastic diplegia

Introduction

Kasabach and Merritt reported the association of thrombocytopenia purpura with the presence of a rapidly enlarging capillary haemangioma in a newborn baby in 1940. Since then, the term Kasabach-Merritt Syndrome (KMS) was used to describe cases that broadly fit the first description.

KMS can be life threatening if haemangiomas involve vital organs like the liver, heart, and brain, or accompanied by thrombocytopenic coagulopathy and/or heart failure. It has been associated with 30-40% mortality as a result of uncontrollable haemorrhage.[1] KMS is clinically heterogenous, the involvement can be cutaneous or visceral, diffuse or multiple.

The development of life-threatening thrombocytopenic consumptive coagulopathy warrants aggressive management.

Management involves initial supporting and stabilizing haemostasis. Consumed clotting factors and platelets are replaced with transfusion of fresh-frozen plasma, cryoprecipitate and platelet concentrates. Surgical removal of haemangioma is hazardous in the presence of uncontrolled consumptive coagulopathy. Other treatments that promote involution of haemangiomas are usually less precarious but take longer time to effect response. Involution therapy with corticosteroids, interferon are commonly practised.

Side effects of interferon treatment are usually mild and transient (e.g. fever and bone pain) and subside with time. However, long term use of interferon in younger children may be associated with irreversible neurological change. We reported a case of spastic diplegia as a result of prolonged use of interferon for the treatment of life-threatening KMS during infancy.

Case Report

LYH was born at term by normal vaginal delivery with a birth weight of 3.39 kg. He was noticed to have large congenital cavernous haemangioma over his left thigh. There were features of bleeding tendency with petechiae and ecchymosis. Hematological investigations during neonatal period confirmed thrombocytopenic coagulopathy. Serial Platelet counts measured between 6-16 x 10^9/L. PT was 15.5 seconds (normal range 11.2-14.1 sec). APTT was

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45.2 seconds (normal range 26.2-40.1 sec). D-Dimer test by Latex Agglutination was >8 ug/ml (normal <0.5 ug/ml). Fibrin degradation product (FDP) was >40 ug/ml (normal <10 ug/ml). Fibrinogen level was 0.94 g/dL (normal range 1.65- 3.63 g/dL). Haemoglobulin level was about 10 g/dL.

Ultrasound of brain was normal, and there was no evidence of intra-cranial haemorrhage.

MRI of abdomen, pelvis, left femur and left leg was performed. There was no hepatosplenomegaly. A large haemangioma involving left thigh and left leg with insinuation between muscle groups of thigh was found. There was no pelvic or abdominal extension. The distended left iliac and femoral vessels suggested hypervascularity as a result of haemangioma.

He was initially treated with supportive transfusion of platelet concentrates, cryoprecipitate, FFP and packed cell in the neonatal intensive care unit. However, clinical improvement was not observed after 2 weeks of prednisolone treatment (dosage 3 mg/kg/day). Another 2 weeks course of high dose prednisolone (~5 mg/kg/day) had been given but without any response. Interferon alpha 2b (3 million units/m^2/day) was started and clinical response was observed one month after treatment. The bluish colour faded and the size of haemangioma over his left thigh decreased. Haematologically , serial platelet counts and the clotting profiles were normalized.

Interferon alpha 2b treatment was given for the first 6 months followed by interferon alpha 2a for another 6 months that resulted in complete involution of haemangioma over left thigh. Dosage of interferon was adjusted according to his updated body surface area (3 million units/m^2/day) during each outpatient clinic follow-up. The cumulative dose of interferon given was 459 million units (Interferon alpha 2a=283 million units and interferon alpha 2b=176 million units).

Tip-toeing gait was first noticed during out-patient follow up at 17 months of age. Neuro-developmental assessment done at 2 years of age showed spastic diplegia and gross motor delay for 9 months. Fine motor was appropriate for age. Hearing and vision were both normal. Verbal language expression and comprehension were appropriate for age.

Repeated out-patient follow up reviewed clumsy gait secondary to his lower limb spasticity and resulted in frequent falls. Examination of his central nervous system and lower back region did not review any abnormality.

MRI brain done at 5 years of age showed no abnormality in the cerebral, cerebellar hemispheres as well as in the brainstem. There is normal white-gray matter differentiation. The ventricles and convexity CSF spaces was normal. There was no evidence of intracranial haemorrhage.

X-Ray of the whole spine showed normal curvature. No focal bony lesion and no disc space narrowing was detected.

MRI Spine done at age of 6 showed normal appearance of the spinal cord and vertebra. No syrinx or intraspinal mass was detected. No tonsillar descent through the foramen magnum.

Discussion

KMS is usually treated with corticosteroid. Patients with KMS responding to corticosteroids usually do so at a dose of prednisolone 2-3 mg/kg/day within a few day.[1-3] However, one-third of patients will be 'non-responders'. Higher doses of 5 mg/kg/day prednisolone[3,4] have been used empirically in such cases. Potential side effects of steroid treatment include gastrointestinal bleeding, immuno-suppression, hypertension and growth retardation. Most treated infants do well and they show catch-up growth after cessation of steroid therapy.

Alternatively, interferon-alpha (α-IFN 2a and 2b) had been used to treat KMS successfully in a large number of steroid non-responders.[5,6]

Its onset of action is generally slower than that of steroid, usually seen within a week or two, but can take up to a month or more. More than half of the patient treated with α-IFN will have some response.[7] The action of interferon alpha was proposed to be an antiangiogenic agent. There was reduction in the urinary excretion of the angiogenic factor bFGF with clinical regression of haemanagioma during α-IFN treatment.[5]

Generally, therapy with α-IFN will be discontinued after a few weeks if no response is seen or continued for several months according to clinical response.[5] Treatment may be continued to more than 12 months in fear of relapse or rebound growth. Common side effects of interferon alpha include fever, irritability, bone pain, neutropenia and abnormalities of liver enzymes. Usually these are transient in nature. In adult population, uncommon yet important side effects of interferon treatment include seizure, acute autonomic and sensory neuropathy, depression , pure red cell aplasia and exacerbation of asthma. They are rarely encountered in children. However, there are recent reports of spastic diplegia in children treated with α-IFN (2a + 2b) during infancy.[8,9]

Our patient LYH was suffering from life threatening KMS as evident by consumptive coagulopathy and

thrombocytopenia. He showed no response to standard and high dose steroid treatment. Haemangioma regressed after 12 months of interferon alpha treatment (3 million units/m^2/day and a cumulative dose of 459 million units) with normalization of his platelet counts and coagulation profiles. Spastic diplegia became evident at 2 years of age. The cause of spastic diplegia was unexplained by his uneventful perinatal course. There was no history of perinatal asphyxia. MRI of brain done at age 5 and MRI spine at age 6 did not review any abnormality. Unfortunately, early MRI brain and spine were not performed at earlier stage which might demonstrate delayed myelination with normal brain parenchyma as a complication of interferon alpha treatment.[9]

Spastic diplegia in children treated with α-IFN (2a and 2b) was reported to be up to 20% of patient.[8-10] With the potential irreversibility of this side effect, interferon should only be reserved for life-threatening cases. The optimal duration of treatment was unknown, but it is preferable to use for shorter periods. Careful and repeated clinical assessment of neuro-developmental status, especially motor development, is mandatory in those interferon treated infants. Clinical signs may include hyper-reflexia of legs with increased tone in the adductors and quadriceps, bilateral unsustained ankle clonus, and extensor plantar responses. While patient is suspended, toes may adopt an extensor posture and legs may extend. On walking, toed-in gait with a tendency to walk on toes may be observed in children with spastic diplegia.

Early stopping of interferon treatment has the potential of reversal of early onset spastic diplegia.[9] If no abnormality is found on MRI of brain and spinal cord, serious consideration of stopping interferon treatment should be made. The decision of continuing interferon treatment should be made when balancing the risk of morbidity from interferon with mortality associated with KMS. When discontinuing interferon treatment is not possible, then a lower dose may be chosen.

Conclusion

Spastic diplegia is associated with interferon alpha treatment for KMS during infancy. Physicians should balance the risk and benefit of interferon treatment. Interferon should be reserved for life-threatening cases only.

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