

Case Report

Safety and Effectiveness of Herbal Medicine Administered from the Early Neonatal Period in Two Neonates with Congenital Cystic Lymphatic Malformations

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Abstract

There are various treatments of lymphatic malformations. Herbal medicine (TJ-28) is effective for treating lymphatic malformations. TJ-28 was administered from the early neonatal period to two neonates with lymphatic malformations at birth. In Case 1, a lymphatic malformation on the neck at birth was treated with TJ-28 from 5 days old. The lymphatic malformation was greatly reduced, but there was a mild transient elevation in liver aminotransferases levels, which were unlikely to be related to TJ-28. In Case 2, a lymphatic malformation in the femur at birth was treated with TJ-28 from 3 days old. There were no adverse events, but the lymphatic malformation was not reduced until 7 months old. TJ-28 administered from the early neonatal period showed no serious adverse events and it was effective in one of two cases. Therefore, TJ-28 may be a treatment for neonates with lymphatic malformations when surgery or sclerotherapy is difficult.

Key words

Herbal medicine; Lymphatic malformation; Neonate; Safety

Introduction

Treatments of lymphatic malformations (LMs) are varied, such as surgery, sclerotherapy, and oral medication.¹⁻³ Recently, the effectiveness of herbal medicine (*Eppikajyutsuto*, TJ-28; Tsumura Co., Tokyo, Japan) in treating LMs was reported.⁴⁻⁶ Whether TJ-28 is safe and effective for administration from the early neonatal period or for neonates with large congenital LMs at birth is unclear. This report describes two neonates with large LMs at birth who were safely treated with TJ-28 from the early neonatal period.

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Received March 22, 2019

Case Report

Case 1

The neonate's mother was 37 years old and had a normal course of pregnancy. A foetal ultrasound and magnetic resonance imaging (MRI) examination showed a mass on the right neck, which suggested LM, at 39 weeks and 4 days of pregnancy. The neonate was delivered at 39 weeks and 5 days of gestation by caesarean section.

The neonate was a boy and his birth weight was 3430 g. The Apgar score was 8 points at 1 minute and 9 points at 5 minutes, and his cardiorespiratory dynamics were stable. He had a mass in the right neck, and it was soft, elastic, and undulating. There were no symptoms of the respiratory tract and oesophageal exclusion. He had no external or internal malformations excluding the mass in the neck. MRI showed a multicystic mass with T1 low intensity and T2 hyperintensity, and this mass was located from the right submandibular to lateral cervical areas (Figures 1A & 1B). The pharynx and airway were retracted and contralaterally deviated. The cyst was diagnosed as mixed micro- and macrocystic LM. Informed consent was obtained from the

patient's parents regarding the fact that the safety and effectiveness of herbal medicine administered in the neonatal period to treat LMs has not been established, and TJ-28 was administered at a dose of 0.2 g/kg/day from the age of 5 days. The patient was discharged home at the age of 7 days.

The patient had no symptoms caused by the LM after discharge. The LM was not complicated by bleeding, infection, or trauma, and was gradually reduced. At 3 months old, apparent swelling of the neck had almost disappeared. MRI showed that the LM was greatly reduced at 5 months old (Figures 1C & 1D). There was a mild increase in liver aminotransferase levels at 5 months of age, and aspartate transaminase was 98 IU/L and alanine transaminase was 94 IU/L; however, both values were maximums at that point and normalised spontaneously by 9 months of age even though administration continued. Therefore, we assessed that this adverse event was not likely related to TJ-28. TJ-28 treatment did not induce pseudoaldosteronism and sympathetic hyperactivity symptoms, and there were no other serious adverse events. TJ-28 administration was stopped at 9 months old. At the time of this report, the patient was 15 months old, and the LM remained, but there was no regrowth. TJ-28 or other additional treatments have not been required.

Case 2

The neonate's mother was 25 years old. A foetal ultrasound and MRI examination showed a mass in the right thigh from 20 weeks of pregnancy. There were no other abnormal findings and no pleural or peritoneal effusion. The neonate was delivered at 39 weeks and 0 day of gestation by vaginal delivery.

The neonate was a boy and his birth weight was 2725 g. The Apgar score was 8 points at 1 minute and 9 points at 5 minutes, and his general condition was stable. He had a mass in the right femur, and it was soft, elastic, and undulating. The circumference of the right thigh was 19 cm and the ratio of right/left was 1.36. MRI showed a multicystic mass with T1 low intensity and T2 hyperintensity, and the mass was located from the right perineum to frontal and interior of the femur (Figures 1E & 1F). The mass was diagnosed as mixed micro- and macrocystic LM. Informed consent was obtained from the patient's parents to use TJ-28, and it was administered at a dose of 0.3 g/kg/day from 3 days old. He was discharged home at 6 days old.

The LM showed no bleeding or infection, but it has not

been reduced to date (Figures 1G & 1H). At the time of this report, the patient was 7 months old, and has been continuing TJ-28 administration. There have been no adverse events, including pseudoaldosteronism and sympathomimetic symptoms. The circumference of the right femur was 32 cm and the ratio of right/left was 1.33.

Discussion

Treatment of LMs has remained a challenge depending on the tumour size, location, and age of onset.¹⁻³ In Japan, the effectiveness of an herbal medicine, TJ-28, has been reported since 2011.⁴⁻⁶ The use and efficacy of TJ-28 in neonates have not been clarified until our report. Furthermore, treatment of large LMs of the neck in infants, particularly early infancy, tend to be surgery or sclerotherapy because of airway obstruction.^{2,3} Sometimes surgery or sclerotherapy is difficult. This is because surgery has the risk of injury to surrounding normal tissues. Sclerotherapy has little effect on some types of LMs and there is the possibility of respiratory obstruction according to reactive enlargement when it is on the neck. New oral therapies, including propranolol, sildenafil, and sirolimus, are effective.¹ However, there is insufficient evidence for the effectiveness of these drugs and serious side effects can occur in a few cases. Caution should be applied for administering these drugs in neonates. Therefore, the current cases were treated with TJ-28 in consideration of safety.

The effect of TJ-28 to LMs is yet to be fully clarified. Mao, which is the main component of TJ-28, suppresses prostaglandin E₂ biosynthesis, expression of cyclooxygenase 2 protein, and activation of the inhibitor of the nuclear factor- κ B-dependent signalling pathway.⁴ These actions might not only reduce the mass, but also prevent bleeding or infection. In one of our cases, the LM was greatly reduced. In the other case, the size of the LM did not decrease, but we continued TJ-28 administration because of the possibility of preventing an increase in the size of the mass, bleeding and infection. Mao is an Ephedra herb and sometimes induces sympathomimetic symptoms. Attention must be paid to tachycardia and hypertension in older people who take Mao, particularly those who have ischaemic heart disease. TJ-28 also contains the *Glycyrrhizae radix*, "Kanzo", so it occasionally induces pseudoaldosteronism. We used TJ-28 while carefully considering the risk of hypertension, tachycardia, oedema,

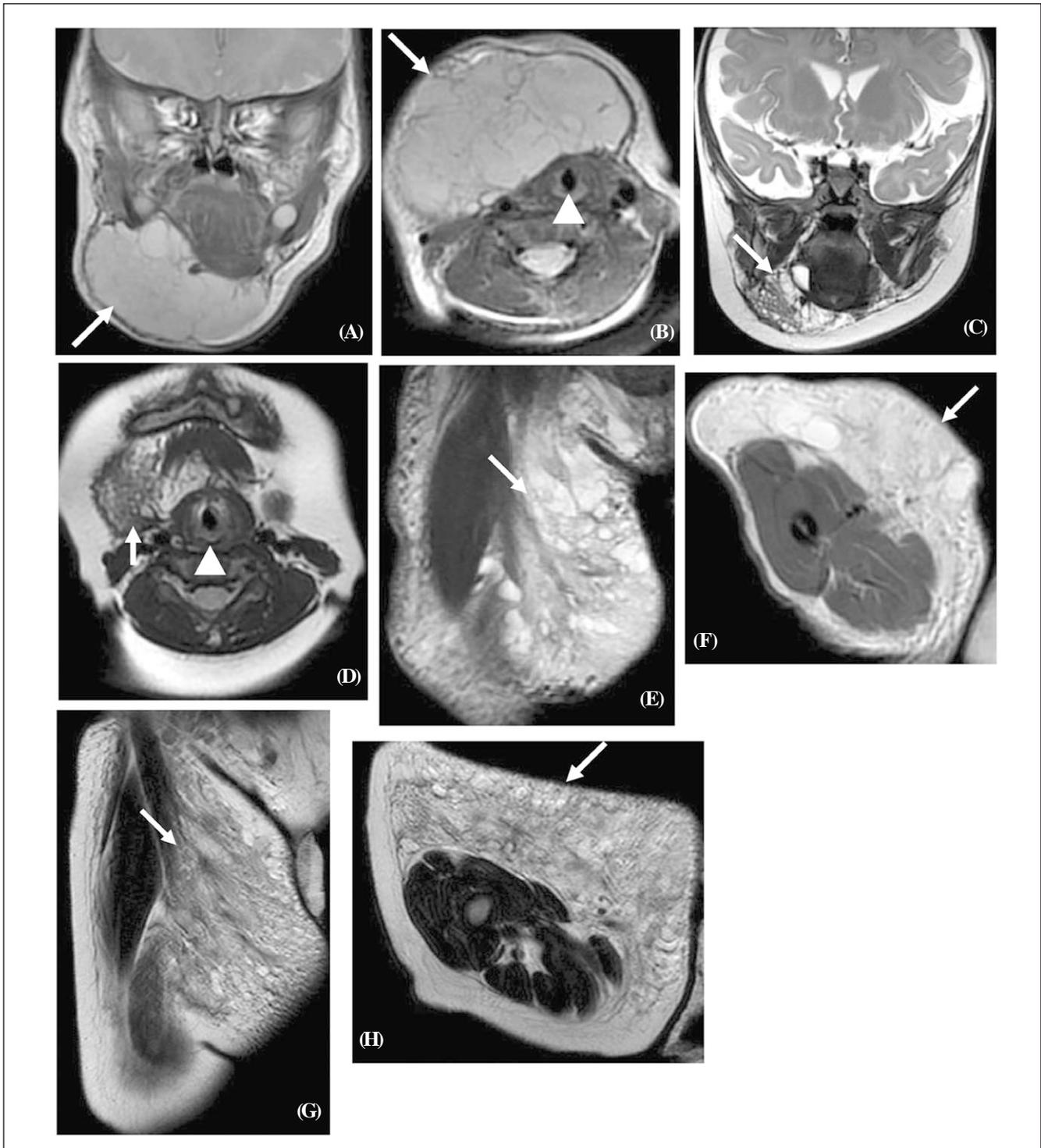


Figure 1 Magnetic resonance imaging (MRI) scan (T2-weighted image).

A, B (Case 1, at birth): MRI shows a large multicystic mass of the neck (*arrow*). The pharynx and airway are retracted and contralaterally deviated (*arrow head*); C, D (Case 1, at 5 months old): The mass shows a marked reduction (*arrow*) and the pharynx and airway are not deviated (*arrow head*); E, F (Case 2, at birth): MRI shows a large multicystic mass of the thigh (*arrow*). The cyst is widely spread from the right perineum to frontal and interior of the femur in subcutaneous tissue; G, H (Case 2, at 5 months old): The mass is not reduced compared with at birth (*arrow*).

irritability and hypokalaemia. There were no serious adverse events, including pseudoaldosteronism and sympathomimetic symptoms, in both of our cases during the administration of TJ-28. Also, the side effects of TJ-28 have not been reported in paediatric patients with LMs. One of our cases showed a mild transient elevation in liver aminotransferase levels; however, this increase was not likely related to TJ-28 treatment. TJ-28 use in neonates is likely safe; however, further studies are needed to confirm its safety.

The most important advantage of TJ-28 therapy for LMs is that it is noninvasive compared with surgery or sclerotherapy, so TJ-28 can be administered as an outpatient treatment. However, the possibility of recurrence after administration, and the optimum dose and duration are unknown. Also, TJ-28 sometimes has a poor effect depending on the location or type.⁴ TJ-28 treatment is more effective for mixed micro- and macrocystic LMs than for macrocystic LMs because TJ-28 prevents the accumulation of lymphatic fluid, and micro- and macrocystic LMs contain less lymphatic fluid than macrocystic LMs.⁴ Additionally, LMs of the head and neck occasionally spontaneously decrease under observation alone.⁷ These factors may explain the different effects of TJ-28 in our two cases. There are still some problems that must be solved regarding TJ-28 therapy for LMs. However, TJ-28 is easy to use in infants, particularly in neonates, who have problems of safety with other treatments. Therefore, TJ-28 should be attempted before surgery or sclerotherapy from the early neonatal period.

In conclusion, TJ-28 treatment from the early neonatal period had no serious adverse events. This treatment was effective for congenital cystic LMs at birth in one of our two cases. In the other case, the LM did not decrease in size, but TJ-28 might have prevented an increase in the size of the mass, bleeding and infection. TJ-28 may be a treatment option for neonates with large LMs when there is difficulty with surgery or with sclerotherapy.

Declaration of Interest

The author declares that there is no conflict of interest.

Declaration of Informed Consent

Informed written consent was obtained in both cases from the patients' parents.

Acknowledgment

We thank Ellen Knapp, PhD, and Jane Charbonneau, DVM, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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