Evaluation of Lymphatic Dysplasia in Patients with Congenital Pleural Effusion and Ascites Using Indocyanine Green Lymphography

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Objectives To investigate the use of indocyanine green (ICG) lymphography in the diagnosis and assessment of the severity of lymphatic dysfunction in infants and neonates with congenital lymphatic pleural effusion and ascites.

Study design We performed ICG lymphography on 10 neonates and infants with congenital lymphatic pleural effusion and ascites. After the subcutaneous injection of ICG, circumferential fluorescent images of lymphatic drainage channels in the extremities and trunk were identified using an infrared camera system. The lymphographic findings were classifiable into 2 patterns—those showing a linear lymphatic pattern, suggesting normal lymphatic flow, and those showing lymphatic channels with retrograde lymphatic flow (dermal backflow pattern), suggesting an abnormal lymphatic flow. We analyzed the severity of the ICG lymphography findings and the clinical outcomes.

Results Based on the ICG lymphography, the severity of lymphatic dysplasia were classified into 4 categories: mild dysplasia, moderate dysplasia, severe dysplasia, and lymphatic hypoplasia. All cases diagnosed with mild (n = 3) or moderate dysplasia (n = 2) survived, and 2 of the 4 cases diagnosed with severe dysplasia died. The duration of endotracheal intubation ranged from 1 to 17 days (median, 7) in the patients with mild or moderate dysplasia and from 25 to 110 days (median, 77) in those with severe dysplasia.

Conclusions The ICG lymphographic findings were consistent with the clinical conditions. This imaging technique may be important to the future clinical management of lymphatic dysplasia in neonates and infants. *(J Pediatr 2014;164:1116-20)*.

Chylothorax and chylous ascites are the accumulation of lymph fluid in the pleural cavity and peritoneal cavity, respectively. The clinical course of congenital chylothorax and chylous ascites varies from spontaneous resolution to death due to the extreme difficulty associated with treatment. In some cases, patients may develop severe respiratory failure or nutritional or immunological deficiency, resulting in death.[1,2] The mortality rate of congenital chylothorax has been high, at 25%-50%.[3-8] In particular, congenital chylothorax and ascites with fetal hydrops are associated with a poor prognosis.[6-8] Nevertheless, the optimal management of these patients has not been well defined, and better treatment strategies could decrease the mortality rate.

Primary lymphatic dysplasia is a congenital maldevelopment of the lymphatic system, in which dysfunction of the lymphatic system may cause leakage of lymph fluid into the limbs and the pleural, pericardial, or peritoneal cavity.[9,10] Lymphoscintigraphic evaluations of newborns and children affected by congenital lymphatic dysplasia were reported to be useful for demonstrating lymphatic vessel impairment.[11-13] However, there are no other adequate methods to evaluate the function of the lymphatic system in neonates and infants. In addition, the pathogenesis of congenital chylous diseases is still poorly understood.

Indocyanine green (ICG) lymphography has been used for the clinical evaluation of lymphedema in adults and is known to be an accurate method that can be used to assess the lymphatic conditions.[14-16] There have been no reports of ICG lymphography in neonates and infants. In this study, we evaluated the use of ICG lymphography for the diagnosis and assessment of the severity of lymphatic dysfunction in 10 neonates and infants with congenital pleural effusion and ascites with a high lymphocyte count (lymphatic pleural effusion and ascites).

Methods

We performed ICG lymphography in patients with congenital pleural effusion and ascites with high lymphocyte numbers (lymphatic pleural effusion and ascites) diagnosed during the prenatal period. The patients were admitted to the neonatal intensive care units of Kanagawa Children's Medical Center and Nagara Medical Center in Japan between March 2011 and May 2013. Lymphatic pleural effusion and ascites were diagnosed based on the

ICG	Indocyanine green
LVA	Lymphaticovenous anastomosis
MCT	Medium-chain triglyceride

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presence of pleural fluid and ascites with a total cell count >1000 cells/mL and a lymphocyte fraction >80%.[17] Infection with rubella virus, toxoplasma, cytomegalovirus, and parvovirus B19 was ruled out, and a negative indirect Coombs test was also demonstrated. We evaluated the maximum volume of lymph fluid drainage per day, the duration of endotracheal intubation, the age at which 100 mL/kg/d enteral feeding was achieved (with a medium-chain triglyceride [MCT] formula), and the total length of the hospital stay as clinical outcomes for each patient. We investigated the relationships between the clinical outcomes and the severity of lymphatic abnormality assessed with the ICG lymphography. This study was approved by the ethics committees of both hospitals, and we obtained written, informed, parental consent.

ICG Lymphography

ICG lymphography (lymphatic channel imaging) was performed as follows: 0.25 mg (0.1 mL) of ICG (Diagnogreen 0.25%; Daiichi Pharmaceutical, Tokyo, Japan) was injected subcutaneously into the second interdigital regions of the hands and the first web space of the feet. After injection, circumferential fluorescent images of the lymphatic drainage channels in the extremities and the trunk were obtained using an infrared camera system (Photodynamic Eye Neo; Hamamatsu Photonics K.K., Hamamatsu, Japan). ICG lymphography was performed at the bedside without sedation (**Video 1**; available at www.jpeds.com). The changes in the fluorescent images over a period of time were observed, and data were recorded immediately, 3-6 hours, and 24 hours after the injection of ICG. The diagnosis of lymphatic dysplasia was based on the lymphographic findings at the time when changes in fluorescent images were no longer observed.

The ICG lymphographic findings were analyzed based on the previous reports of cases of lymphedema in adults.[17-19] We classified the images of ICG lymphography into 2 categories for evaluation: those showing a linear pattern, suggesting normal lymphatic flow, and those showing a dermal backflow pattern, suggesting an abnormal filling of the lymph capillaries. In the normal extremities, a linear lymphatic channel (linear pattern) is demonstrated on ICG lymphography, which reflects smooth lymphatic flow (**Figure**, A, and **Video 2**; **Video 2** available at www.jpeds.com). In contrast, in the extremities of patients with a lymphatic problem, ICG lymphography shows a dermal backflow pattern, which reflects retrograde lymphatic flow from occluded upstream lymphatic vessels, thus leading to the backflow of lymph into the lymph capillaries of the skin from the collecting lymphatic vessels (**Figure**, B and C, and **Video 3**; **Video 3** available at www.jpeds.com).[17-19]

Results

Ten patients were identified who had a fetal diagnosis of congenital lymphatic pleural effusion or ascites between March 2011 and May 2013 (**Table I**; available at www.jpeds.com). Chromosomal abnormalities were recognized in 4 of 10 patients. Atrial ectopic tachycardia was observed in case 7; no other major organ abnormality was present. Fetal hydrops with peripheral adema at birth was present in 8 of the 10 patients. Six patients had both ascites and pleural effusion, 2 had only ascites, and 2 had only pleural effusion. All patients required immediate intervention with mechanical ventilation after birth due to respiratory failure.

The strategy for medical care after birth that we used was as follows: for patients with pleural effusion, continuous drainage was performed, and total parenteral nutrition with a percutaneous central venous line was initiated and maintained until resolution. Octreotide, with or without prednisolone, was commenced if the volume of drainage was >50-100 mL/d after 7-14 days. If there was no improvement with this treatment, a pleuroperitoneal shunt was implanted or microsurgery was performed. Microsurgery with lymphaticovenous anastomosis (LVA) was performed in cases 8-10 on day 87, day 51, and 6 months after birth, respectively. Enteral feeding with an MCT formula was not initiated, and fasting was maintained until resolution of the pleural effusion.

ICG Lymphography and Clinical Outcomes

According to the severity of the ICG lymphographic findings of the extremities, the severity of lymphatic dysplasia for each patient was classified into 1 of 4 categories: mild lymphatic dysplasia, moderate lymphatic dysplasia, severe lymphatic dysplasia, or lymphatic hypoplasia (**Figure** and **Table II**). In cases 1-3, ICG lymphography demonstrated a linear pattern without any obvious dermal backflow pattern; these were classified as having mild lymphatic dysplasia (**Figure**, A). In cases 4 and 5, there was a combination of normal and abnormal findings (ie, a linear pattern was seen in some areas of extremities, and a dermal backflow pattern was apparent in the some areas of extremities, external genitalia, and trunk) (**Figure**, B); these were considered to have moderate lymphatic dysplasia. Cases 6-9 were considered to have severe lymphatic dysplasia, because a linear pattern was hardly seen but a diffuse dermal backflow pattern was demonstrated over wide areas from the extremities to the trunk (**Figure**, C, and **Video 3**). Case 10 was considered to have lymphatic hypoplasia. In Case 10, ICG was injected subcutaneously into the left lower limb where severe edema was present, but lymph flow in the left lower limb was hardly observed during the observation period, even after 24 hours had passed.

Table I summarizes the severity of the ICG lymphographic findings and clinical outcomes in each case. All of the cases who were diagnosed as having mild or moderate lymphatic dysplasia based on the ICG lymphography survived (cases 1-3 as mild dysplasia, cases 4 and 5 as moderate dysplasia), and 2 of the 4 cases diagnosed with severe dysplasia died (cases 8 and 9). The duration of endotracheal intubation was 1-7 days in cases diagnosed with mild lymphatic dysplasia, 8 and 17 days in cases with moderate dysplasia, and 25-110 days in cases with severe dysplasia. The age at which 100 mL/kg/d enteral feeding was achieved was 8-27 days in cases diagnosed with mild lymphatic dysplasia, 28 and 44 days in cases with moderate dysplasia, and