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CASE REPORT

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# Trametinib restores the central conducting lymphatic flow in a premature infant with Noonan syndrome

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**Key Clinical Message**

We describe a premature hydropic infant with Noonan syndrome and a therapy refractory chylothorax. This was shown to be due to a central conducting lymphatic anomaly. After therapy with a MEK-inhibitor the infant recovered clinically and radiologically completely, possibly by restoring lymphatic valve function.

**KEYWORDS**

CCLA, DCMRL, MEK-inhibition, Noonan syndrome, RAS/MAPK pathway

## 1 | INTRODUCTION

Noonan syndrome (NS) is mostly an autosomal-dominant disorder, characterized by typical facial features, congenital heart defects and lymphatic disease.[1] Pathogenic activating germline variants in multiple genes encoding components of the Rat sarcoma/Mitogen-Activated Protein Kinase pathway (RAS/MAPK pathway) have been shown to be involved in NS, of which variants in *PTPN11* occur in about 50%–60% of patients.[1] The RAS/MAPK pathway is suggested to play a key role in the development of the lymphatic system, and can lead to lymphatic diseases such as hydrops, chylothorax, protein losing enteropathy and lymphedema. The prevalence of lymphatic disease in NS is estimated to be 37% during lifetime.[2] The underlying mechanism may be an abnormal development of the central lymphatic system leading to a central conducting lymphatic anomaly (CCLA).[3] CCLA affects large lymphatic vessels in the middle of the torso, resulting in central flow problems and subsequent backward flow or leakage of lymph fluid. One of the most prevalent presentations in infancy is chylothorax, which can be refractory to standard therapy.[2–4] Inhibition of the RAS/MAPK pathway by mitogen-activated protein kinase-inhibition (MEK-inhibition) has been shown to be a potential treatment for refractory chylothorax in patients with NS and CCLA.[4] In this article we describe the clinical and radiological results of treatment with the MEK inhibitor trametinib in a hydropic premature infant with NS and bilateral therapy resistant chylothorax.

### 1.1 | Case history

The boy was born after 31 + 4 weeks of gestation by cesarean section. The gestation was complicated by fetal hydrops, bilateral hydrothorax and polyhydramnios, for which amniocentesis was performed at a gestational age of 29 + 6 weeks. Genetic tests showed he was a carrier of a familial pathogenic variant in *PTPN11* (c.922A>G; p.(Asn308Asp)). Due to an impending preterm delivery corticosteroids were given. At birth, the infant was in respiratory distress and required endotracheal intubation and 100% supplemental oxygen. His birth weight was 2.37 kg (SDS>2.5). The chest x-ray showed bilateral hydrothorax, more severe on the right side, where a chest tube was placed. A congenital heart defect could be excluded by echocardiography. After 3 days, the suspected diagnosis chylothorax could be confirmed based on the changing color of the pleural fluid and technical analysis. For this reason, his diet was modified to a medium-chain triglyceride-based diet, which was replaced after 1 week by total parenteral nutrition due to massive chylous production (>250 mL/day). Also, octreotide was started at the age of 2 weeks. Chylous production continued, and after 3 weeks the chylothorax on the left deteriorated, for which a second chest tube was placed. The chylous production continued to be 300–350 mL/24 h, causing low serum albumin (for which albumin infusions were given), immunodeficiency consisting of lymphopenia (for which *pneumocystis jiirovecii* prophylaxis was given) and low IgG (for which intravenous immunoglobulins were given), and low thyroid hormone levels (for which levothyroxine treatment was given).

## 2 | METHODS

At this moment the differential diagnosis was: isolated refractory bilateral chylothorax in an infant with NS or refractory bilateral chylothorax caused by a CCLA in an infant with NS. Due to lack of improvement with standard care, the patient was referred to our center at the age of 23 days for Dynamic Contrast-enhanced MR Lymphangiography (DCMRL) and, if possible, targeted therapy with MEK-inhibitor trametinib.[3–5]

DCMRL is performed by injecting gadolinium-based contrast agent into inguinal lymph nodes and following the propagation of the contrast. The DCMRL showed slight antegrade retroperitoneal lymph flow until the level of the kidneys. No cisterna chyli and thoracic duct could be shown. However, there was massive dermal backflow at both sides and retrograde penile and scrotal contrast flow (Figure 1). It was possible that the lymph flow was too slow and/or too little to fill the antegrade lymph vessels on DCMRL. However, the massive retrograde flow combined with the incidence of CCLA in patients with NS made a diagnosis of CCLA more likely.

Although therapeutic interventions so far had failed to reduce the chylous effusions, these were continued. Octreotide was discontinued due to national manufacturing problems. Propranolol was started while waiting for approval for treatment with trametinib. After parental consent and formal permission of the Health and Youth Care Inspectorate, treatment with off-label use of trametinib suspension (provided as compassionate use by Novartis Pharmaceuticals as a liquid suspension)

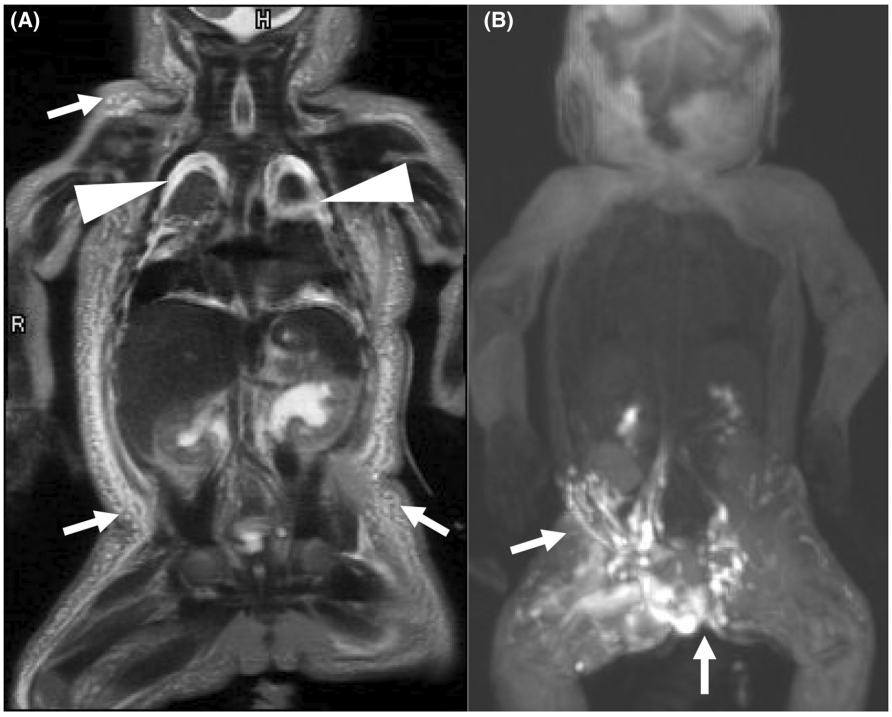


**FIGURE 1** Dynamic Contrast-enhanced MR Lymphangiography prior to treatment with trametinib. (A) Coronal T2 weighted image, with arrows indicating the subcutaneous edema and arrow heads indicating the pleural fluid. (B) Coronal T1 weighted MR image after intranodal contrast injection. The arrows indicate the dermal backflow of the lymphatic contrast. There is no contrast enhancement of the thoracic duct.

was started. Initially, at a dose of 0.0125 mg/day once every other day, followed by an increase to 0.0125 mg daily after the first two weeks. After 8 days the trametinib and propranolol were ceased due to an urosepsis with *Escherichia Coli*. After 6 days trametinib could be restarted, while propranolol was not due to persistent low blood pressure.

### 2.1 | Outcome and follow-up

Twenty-three days after the initial start of trametinib, the right chest tube could be removed, 38 days after initial start of trametinib the left chest tube could be removed as well. Four days later the infant could be weaned from positive pressure mechanical ventilation (42 days after start trametinib, in total 65 days ventilated). Enteral feeding with a medium-chain triglyceride-based diet was started again, 28 days after the initial start of trametinib, and total parenteral nutrition could be stopped 45 days after the initial start of trametinib. At the age of 3 months breast milk was started in increasing amounts. *Pneumocystis jiirovecii* prophylaxis and transfusion of immunoglobulins could be stopped. Just before the age of 6 months, the hydrops had disappeared and he was discharged home. The maximum administered dose of trametinib was 0.018 mg/kg/day.

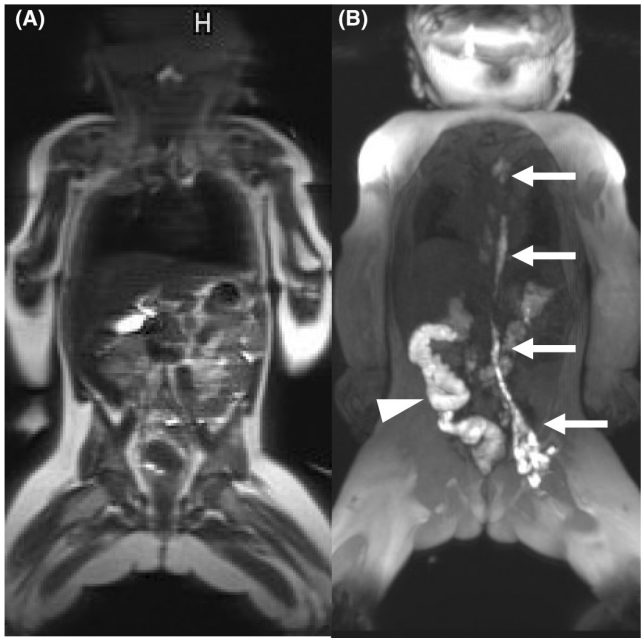


**FIGURE 2** Dynamic Contrast-enhanced MR Lymphangiography after treatment with trametinib. (A) Coronal T2 weighted image, now without subcutaneous edema or pleural fluid. (B) Coronal T1 weighted MR image after intranodal contrast injection. The arrows indicate the contrast in the iliac lymphatic vessels and the thoracic duct. The arrrow head indicates a normal bowel. There is no dermal backflow.

Laboratory follow up showed a maximum AST 91 U/L (ref <35 U/L) and maximum ALT 42 U/L (ref <45 U/L). Serial echocardiograms showed no development of hypertrophic cardiomyopathy over the course of 18 months. The only possible adverse event was the development of constitutional eczema, which could be treated with (corticoid) ointments. At the age of 11 months, a second DCMRL was performed showing normal antegrade flow in the iliac lymphatic vessels and the appearance of a normal thoracic duct. There was no dermal backflow (Figure 2). The trametinib was stopped at the age of 12 months. At the age of 18 months, he has no recurrence of chylothorax and hydrops.

## 3 | DISCUSSION

Lymphatic disease are common in patients with NS and are caused by germline gain-of-function variants in genes encoding components of the RAS/MAPK pathway. Also somatic variants in these genes have been identified in patients with complex lymphatic anomalies.

Due to recent innovative diagnostics as DCMRL, it has become evident that lymphatic disease may be due to CCLA in patients with NS. In seven out of 10 children described by Biko et al. in whom a DCRML was performed, the thoracic duct was not present in four, rudimental in one, duplicated in one and dilated but present in one child.[6] Classically, severe congenital chylothorax is symptomatically treated by pleural drainage. This is often combined with diet modification to reduce chylous production. Pharmacological treatments include octreotide and propranolol.[7,8] Until recently, with the use of MEK-inhibition, no treatment was available targeting the underlying pathophysiological mechanism.

Because the RAS-MAPK pathway is a well-known drug target in cancer, several small molecule inhibitors have been repurposed for use in lymphatic malformations and complex lymphatic anomalies. Trametinib, a highly selective inhibitor of MEK1/2, was first approved in 2013 for the treatment of BRAF V600E mutated metastatic melanoma. Since then, the drug has been approved for several other indications.[9] Trametinib as a therapeutic agent for patients with NS and CCLA has been described in several case reports. However, only four case reports so far have reported on both the clinical and radiological follow-up, with DCMRL, after treatment in patients with NS.

Li et al. described a 12-year old boy with recurrent chylopericardium, chylothorax and lymphedema that was not responding to conventional treatment with sirolimus.[10] The DCMRL showed a dilated lumbar lymphatic

network with a dilated and tortuous thoracic duct, and retrograde flow into the liver, mediastinum, pericardium and genitals. Genetic testing revealed a pathogenic variant in *ARAF* (c.640T>C; p.S214P), leading to hyperactivation of RAS/MAPK pathway. Treatment with trametinib was started 4 months after sirolimus was discontinued and resulted in a dramatic clinical improvement with remodeling of the lymphatic system and near normalization of daily activities. Twelve months after start of trametinib the DCMRL showed resorption of the subcutaneous ducts, with formation of a new, more normal-appearing lymphatic system along the abdominal wall into the thorax.

A case of a girl with NS due to a pathogenic variant in *SOS1* (c.2536G>A; p.Glu846Lys) was published by Dori et al. The patient presented with persistent chylothorax at the age of 5 years old and protein-losing enteropathy at the age of 14. DCMRL revealed a diffusely abnormal central lymphatic system with retrograde mesenteric flow. After 8 weeks of treatment with trametinib her symptoms resolved. After 3 months, a second DCMRL was performed where complete remodeling of the central lymphatic system was described.[11]

In an article by Nakano et al.,[4] two cases were described. First a 3-month old girl with NS due to a pathogenic variant in *SOS1* (c.1322G>A; pCys441Tyr) with bilateral chylothorax and ascites after surgery. DCMRL was performed and showed dilated and malformed lymphatics in the bilateral hila, intercostal spaces and lungs. Within 1 month of starting therapy with trametinib, the patient was weaned off ventilatory support and chest tubes could be removed. Repeat DCMRL demonstrated a more efficient use of the thoracic duct with decreased use of collateral vessels. The second patient is a female with NS due to a pathogenic variant in *RIT1* (c.246T>G, p.Phe82Leu). The patient, born with a severe hypertrophic cardiomyopathy, developed life-threatening refractory bilateral chylous effusions after cardiac surgery. DCMRL demonstrated a CCLA with dilated lymphatic vessels.[4] Trametinib was started and within 1 month of the start of therapy, the chest tube was removed. The patient was able to wean off positive-pressure ventilation and was discharged to outpatient management. Repeat DCMRL demonstrated a small amount of residual fluid with improved dilation of her central lymphatics.

In three of these four cases a (complete) remodeling of the lymphatic system is described after treatment with trametinib. In our patient, we did not see remodeling of the central lymphatic system. However, we did see cessation of retrograde flow with the appearance of normal flow in the thoracic duct and normalization of lymphatic drainage. Together with the previously published cases we can define lymphatic remodeling as a significant change in the central lymphatic system, resulting in a functional improvement or normalization of lymphatic flow and drainage.

The precise mechanism by which trametinib improves lymphatic function is not known. Previous studies showed that hyperactive RAS signaling affects the maturation of lymphatic vessels, leading to dilated lymphatic channels, and impairs the formation and maintenance of lymphatic valves, leading to valve regression.[12,13] Trametinib has been shown to prevent the disintegration of lymphatic valves in mice harboring a pathogenic KRAS variant and to decrease the diameter of lymphatic vessels in mice embryos.[12,14] These findings reveal possible mechanisms by which trametinib could improve lymphatic function in patients with RAS pathway–activating variants. However, due to the complex nature of lymphangiogenesis and the various pathways involved, the precise pathophysiological mechanisms remains to be determined. In our case, the functional improvement could be explained by the restoration of lymphatic valve function.

Our case adds to the current state of evidence that MEK-inhibition is effective in infants with NS and refractory lymphatic disease. The optimal dosage and duration of treatment is not known. Due to the prematurity and young age of our patient, we did not start with the daily dose of 0.02–0.027 as suggested in previous reported cases.[15] Our maximum dose was 0.018 mg/kg/day, which was effective. However, larger studies are needed to establish the optimal dosage and treatment duration.

## AUTHOR CONTRIBUTIONS

**Erika K. S. M. Leenders:** Conceptualization; writing – original draft; writing – review and editing. **Lotte E. R. Kleimeier:** Conceptualization; writing – original draft; writing – review and editing. **Lauren C. Weeke:** Conceptualization; data curation; writing – original draft; writing – review and editing. **Catelijne H. Coppens:** Conceptualization; writing – original draft; writing – review and editing. **Willemijn M. Klein:** Conceptualization; data curation; writing – original draft; writing – review and editing. **Jos M. T. Draaisma:** Conceptualization; supervision; writing – original draft; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

All authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

## ETHICS STATEMENT

Written informed consent was obtained from both parents of the patient for use of data and publication of medical data and images.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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