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ORIGINAL ARTICLE

Pulmonary involvement in Niemann-Pick C type 1

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Abstract

Niemann-Pick disease type C (NPC) is a lysosomal storage disorder caused by mutations in either NPC-1 or NPC-2 genes, resulting in abnormal intracellular cholesterol trafficking. The estimated prevalence of NPC disease is 1: 120,000–150,000. Lung involvement has been described in only few patients with NPC, mostly NPC2. We describe a series of 12 patients, originating from six families all homozygotes to the *p.R404Q* (*c.1211G > A*) mutation of *NPC1* gene; nine of them had significant pulmonary manifestations. All patients were followed in our medical center. Nine of the patients had pulmonary involvement, with recurrent pneumonia as the first manifestation in most, followed by recurrent wheezing episodes and subsequent development of interstitial lung disease with chronic need for oxygen support. Seven patients were reported of having interstitial disease by various imaging modalities.

Conclusion: Pulmonary involvement in NPC1 is more common than previously reported. It is characterized as primary obstructive and restrictive lung disease and not only as part of neurologic sequel of NPC. It can lead to respiratory insufficiency and death from respiratory failure.

What is Known:
- *Lung involvement has been described in only few patients with NPC.*
- *Most reported NPC cases with pulmonary involvement were of NPC2.*

What is New:
- *Pulmonary involvement in NPC1 is more common than previously reported.*
- *Pulmonary involvement in NPC1 should be considered as part of the disease and be thoroughly assessed and managed.*

Keywords Niemann-Pick C1 disease · Cholesterol trafficking · Pulmonary involvement · Mutation *R404Q* · Respiratory failure

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Abbreviations

EM	Electron microscope
LAMP1	Lysosomal associated membrane protein 1
NPC	Niemann-Pick disease type C
PFTs	Pulmonary function tests
VSGP	Vertical supranuclear gaze palsy
BAL	Bronchoalveolar lavage
CT	Computerized tomography

Introduction

Niemann-Pick type C (NPC) disease is a lysosomal storage disorder caused by a primary defect of cholesterol trafficking leading to abnormal cholesterol esterification.

The estimated prevalence of NPC (MIM# 257220) is 1: 120,000–150,000 [18, 24, 26].

There are four phenotypic types of NPC in reference to neurological onset, all preceded by systemic involvement: early infantile—presents with early jaundice with or

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without liver dysfunction that mostly resolves, and a later development of progressive neurological deterioration that leads eventually to early death, during the first years of life. Late infantile—presents with language delay, gait problems, hearing loss, vertical supranuclear gaze palsy, cataplexy with development of seizures and worsening ataxia, and dementia. Juvenile—the commonest form which occurs in mid-to-late childhood with the insidious onset of ataxia, school difficulties and loss of daily motor abilities, deteriorating to seizures, and dementia. Adult onset—which presents with dementia or psychiatric symptoms [24]. An exception is the rapidly fatal neonatal that usually succumb before 6 months of age. However, there is a great overlapping spectrum of presentations and often patients are discovered due to asymptomatic splenomegaly [24].

The diagnosis of NPC based on clinical suspicion is done biochemically by filipin staining which demonstrates the free cholesterol storage in fibroblasts, and genetically by molecular mutation analysis. Two genes are involved in NPC: the common one, *NPC1*, which accounts for approximately 95% of NPC cases, is mapped to 18q and codes for a 1278 amino acids containing protein. NPC1 protein is localized to the late endosomal membrane and is involved in cholesterol trafficking. The second gene, *NPC2*, accounts for 4% of NPC cases and has been mapped to 14q24.3. It encodes for a 132 amino acids containing protein. NPC2 mainly co-localizes with lysosomal associated membrane protein 1 (LAMP1) but is also distributed to LAMP1-negative organelles [25].

Regulation of cholesterol homeostasis is especially important for alveolar type II cells. These cells are responsible for surfactant production, storage, and release. The actual storage areas are the intracellular lamellar bodies. The release of surfactant is by exocytosis. Surfactant is composed of lipids and proteins. Its primary function is reduction of surface tension in the alveoli, and cholesterol in the appropriate ratio is a critical component for accomplishing it [1, 10]. The NPC pathway, composed by the NPC protein 1, a large transmembrane protein, and NPC protein 2, a soluble lysosomal protein, has an important role in intracellular trafficking of cholesterol. Therefore, blocking of this pathway, whether by impaired *NPC1* or *NPC2* genes, would lead to disruption of cholesterol trafficking and as a result to accumulation of cholesterol within type 2 pneumocytes and alveolar macrophages [20].

Lung involvement has been described in a few patients with NPC, mostly *NPC2*. It was clinically expressed as alveolar proteinosis [2, 8]. In animal studies, Liu et al. showed that mice lacking NPC1 function had lungs heavily infiltrated with macrophages and cholesterol [11].

We describe here a series of 12 patients, originating from six expanded families, all homozygous to the p.*R404Q* (*c.1211G > A*) mutation of *NPC1* gene; nine of them had significant pulmonary manifestations.

Patients and methods

Data was collected from patients' historic and current medical files. All patients were diagnosed with NPC by mutation analysis of the NPC1 gene in our medical center.

The study was approved by the ethics committee of Soroka Medical Center.

All the patients described here were of Bedouin origin and belonged to a small number of clans.

Data collection has been focused on visceral and neurologic manifestations, respiratory involvement, and imaging studies.

Results

Clinical and demographic features of the patients are summarized in Table 1.

Twelve patients from six nuclear families were included in the study. Eleven patients were a result of a consanguineous marriage, and eight of the patients also had affected siblings. In addition, as can be seen in the family tree in Fig. 1, six of the patients originated from the same inter-related family. Two patients were diagnosed prenatally but their families declined pregnancy termination. All of our patients presented within the first 2 months of life. Six patients presented at the neonatal period with jaundice. Hepatosplenomegaly and failure to thrive were the common findings during infancy and early childhood. Hepatosplenomegaly was persistent in all patients; however, cholestasis resolved in seven patients. Six patients had ascites in varying degrees of severity, and developmental delay and neurologic regressions were seen later in surviving patients (Table 1).

Nine patients (75%) suffered from pulmonary involvement. Pulmonary involvement in most patients started at a very early age (age range 3 months–4.5 years). In six patients (67%), it appeared during the first 2 years of life. Patient 12 has suffered from bronchopulmonary dysplasia due to prematurity. Nine patients (75%) have died before 5 years of age. The patients presented with tachypnea, and crackles were found on auscultation during their first physical examination. The clinical presentation was recurrent pneumonia accompanied by recurrent wheezing episodes and the later development of interstitial lung disease with chronic need for oxygen support (Table 2). Seven patients were reported of having interstitial disease by various imaging modalities, such as chest X-rays and computerized tomography (CT). All of the patients were treated with short courses of bronchodilators and oxygen occasionally.

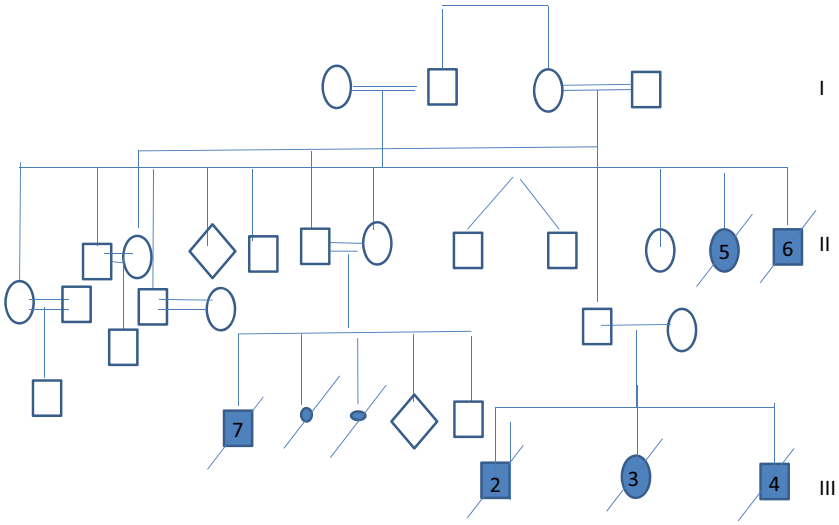
Patient 3 illustrates the typical pulmonary involvement in our patients (Fig. 2). This patient was born after an uncomplicated pregnancy and was discharged home after 48 h. He developed cholesthatic jaundice immediately after birth which

Table 1 Patients' presentations

Clan/ family	Pt	Initial presentation	Age at pre.	Hepatosplenomegaly	Cholesthasis resolved (age)	Liver failure	Lung involvement	Neurology pre. (age)	Neurology pre.	Death (age)
1	1	Neonatal jaundice + UTI	Birth	Yes	–	Yes	Yes	–	–	4 months
2-I	2	Hepatosplenomegaly	Birth	Yes	3.5 years	No	No	3.5 years	Dev. delay + regression	6.5 years
2-I	3	Neonatal jaundice	Birth	Yes	3 months	No	Yes	3 months	Dev. delay	3 years and 4 months
2-I	4	Hepatosplenomegaly Neonatal jaundice+	2 months	Yes	1.5 years	No	Yes	3 years	Dev. delay + regression	5 years and 7 months
2-II	5	Hepatosplenomegaly	2.5 months	Yes	1 year	No	Yes	1 year	Dev. delay + regression	2 years and 11 months
2-II	6	Neonatal jaundice	Birth	Yes	No	No	Yes	2 years	Dev. delay + regression	4 years and 5 months
2-III	7	Hepatosplenomegaly + vomiting	2 months	Yes	1.5 years	No	No	2 years	Dev. delay + regression	3 years and 10 months
3	8	Neonatal jaundice	Birth	Yes	No	Yes	No	–	–	3 months
4	9	Hepatosplenomegaly Neonatal jaundice+	Birth	Yes	6 years	No	Yes	5 years	Dev. delay + regression	5 years and 4 months
4	10	Hepatosplenomegaly + failure to thrive	8 months	Yes	2 years	No	Yes	1.5 years	Dev. delay + regression	4 years and 4 months
5	11	Neonatal jaundice	Birth	Yes	No	Yes	No	–	–	2.5 months
6	12	Hepatosplenomegaly	2 months	Yes	1 year	No	Yes	2.5 years	Dev. delay + regression	3 years and 11 months

PRE presentations; *DEV* developmental

Fig. 1 Family 2 pedigree



resolved when he was 3 months old. When he was 2 months old, he developed hepatosplenomegaly, and later failure to thrive and developmental delay with regression, as presented in Table 1.

At 2 years of age, he presented with respiratory distress and hypoxemia that necessitated recurrent admissions. Lung auscultation revealed short and labored inspiration with rhonchi and rales on both lung fields. Nails clubbing was also noted. Chest X-ray revealed bilateral increased interstitial markings with bilateral basal alveolar infiltrates. Cardiac echo revealed normal anatomy and function and no pulmonary hypertension. Chest CT revealed bilateral enlarged alveolar infiltrates at lung bases, with extensive interstitial involvement (Fig. 2e, f). Flexible bronchoscopy showed normal anatomy with only scant milky secretion. Cultures for viral, bacterial, and fungal pathogens were all negative. Broncho alveolar lavage (BAL) was positive for foamy macrophages and EM staining showed abundant polymorphous cytoplasmic inclusion bodies (Fig. 2c, d). The patient kept deteriorating and needed tracheostomy. A trial with whole lung lavage did not improve his clinical condition and he succumbed to death at the age of 4 years and 3 months due to respiratory failure.

BAL and postmortem investigations were performed only in patient 3.

Table 2 Pulmonary manifestations

Family	Patient	Age at presentation	Pulmonary manifestation	Treatment
1	1	3 months	Interstitial lung disease	Oxygen, antibiotics, bronchodilators
2-I	2	4 months	Recurrent wheezing and chest deformations, interstitial lung disease	Bronchodilators and oxygen
2-I	3	1 year	Interstitial lung disease	Oxygen, antibiotics, bronchodilators
2-I	4	3 years + 10 months	Recurrent pneumonia and recurrent wheezing, interstitial lung disease	Bronchodilators and oxygen
2-II	5	1 year + 2 months	Recurrent wheezing and pectus excavatum-restrictive disease, interstitial lung disease	Bronchodilators and oxygen
2-II	6	3 years + 7 months	Recurrent wheezing and barrel chest, interstitial lung disease	Bronchodilators and oxygen
4	9	4 years + 6 months	Recurrent pneumonia and recurrent wheezing	Oxygen, antibiotics, bronchodilators
4	10	1 year + 1 month	Recurrent wheezing	Bronchodilators and oxygen
6	12	1 year + 3 months	Recurrent wheezing, interstitial lung disease	Bronchodilators and oxygen

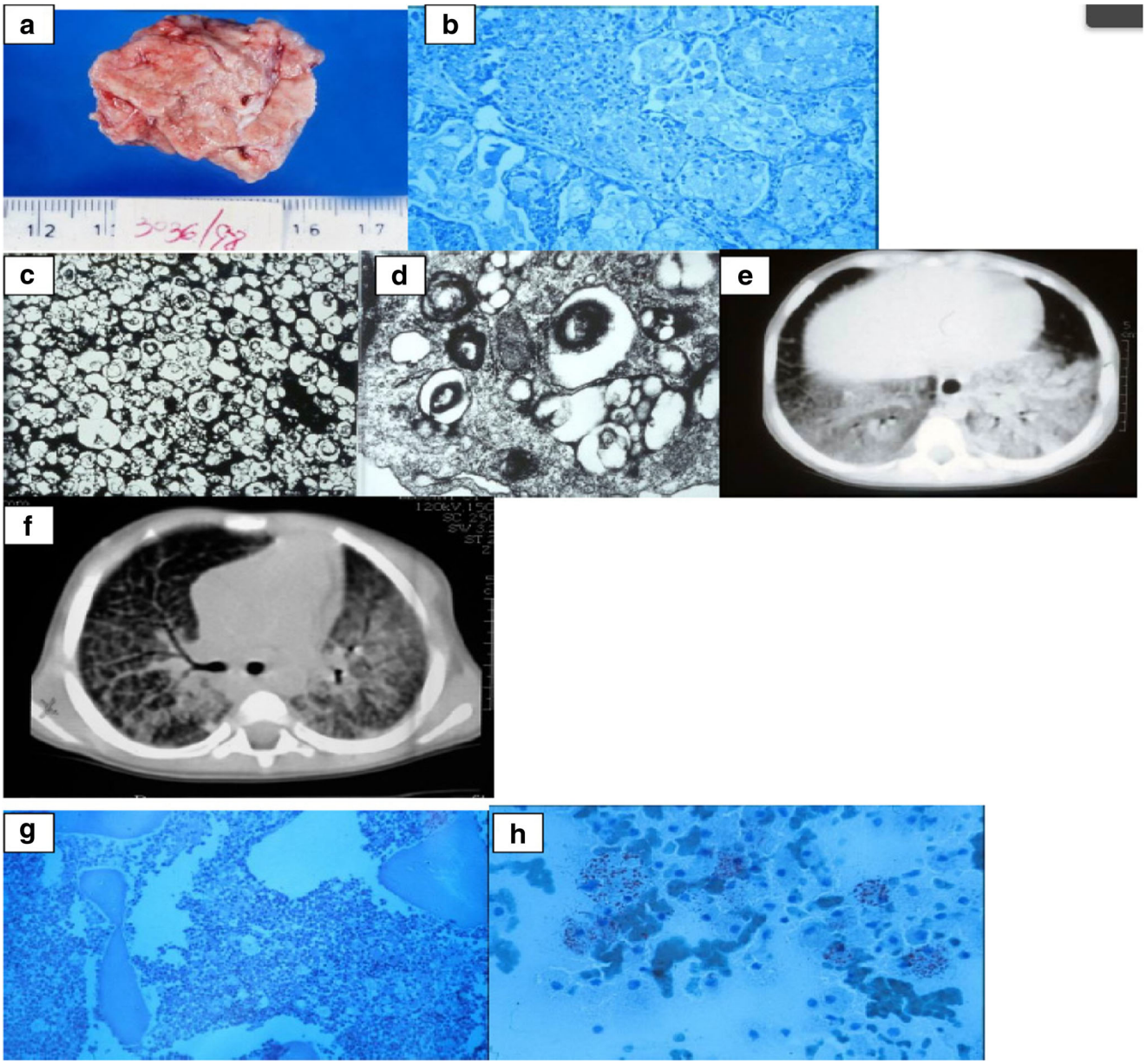


Fig. 2 Patient 3. **a** Lung postmortem–gross pathology. **b** Lung postmortem–lung pathology showing massive infiltration of the alveoli and the interlobular septate with large foamy macrophages, chronic inflammation, and no hyaline membrane or lung fibrosis. **c** Alveolar macrophage–multiple polymorphous cytoplasmic inclusion bodies (PCBs) (× 4500). **d** BAL: alveolar macrophages-foamy cells–multiple polymorphous cytoplasmic inclusion bodies (PCBs) (× 30,000). **e** Pulmonary computed tomography–diffuse alveolar infiltrates at both lung fields. **f** Computed tomography-carina level–increased interlobular thickening. **g** Bone marrow histology-rib–foamy cells. **h** Lung histology-alveolar macrophages–foamy cells

On postmortem, his lungs showed massive infiltration of the alveoli and the interlobular septa with large foamy macrophages, chronic inflammation, and no hyaline membrane or lung fibrosis.

Discussion

We described a relatively large number of genetically homogenous group of NPC1 patients. All patients were homozygous for the same *NPC1* gene mutation p.*R404Q*. The mutation is easily detected using an *MspI* restriction analysis [13]. This mutation has been previously reported as heterozygous in different ethnicities, such as Japanese and mixed Europeans. The reported patients had early infantile type. However, lung involvement was not reported [14, 17, 27, 28].

Nine of our 12 patients have developed progressive pulmonary involvement with recurrent wheezing episodes and interstitial lung pattern on chest imaging. Infant's pulmonary function tests (PFTs) were not available at our center and the

patient was too sick to perform regular PFTs later in their life. All patients presented quite early with tachypnea, crackles, and wheezing. We noticed that bronchodilators did not ameliorate their symptoms. Of note, Bedouin children treated in our pulmonary clinic are not prone to the best of our knowledge to inherited interstitial lung diseases, and therefore, a search for such conditions was not performed.

Wheezing episodes that occur repeatedly can be seen in up to 19% of all children [12]. The underlying pathology is small airways narrowing, and the resolution occurs due to the growth of the airways. Indeed, these children (like our group) demonstrate hyperinflation and wheeze. However, the prolonged periods of hypoxemia are a pattern that is not consistent with reactive airway disease. Neither is the fact that they did not respond to bronchodilators.

On the other hand, the findings in our patients raise the question of interstitial lung disease. This condition is always suspected when you have the triad of tachypnea, hypoxemia, and fine crackles.

Wheezing occurs in 20% of patients with pediatric interstitial lung disease [5]. The pathophysiology mainly is intrathoracic airway obstruction [3].

The estimated incidence is 0.36/100,000 children [6]. Seventy five percent of all cases present before the patient of 1 year of age, as it was in our cohort.

We suggest that the presentation of wheezing, tachypnea, and in most patient fine crackles, followed by prolonged periods of hypoxemia can be explained by an interstitial disease that was caused by the accumulation of foamy material within the alveoli. This was demonstrated in patient 3 whose clinical course well represents our group of patients.

We tried a whole lung lavage as a last resort, based on our clinical experience with previous patients with a similar picture of unexplained tachypnea and hypoxemia, in the setting of a rapid pulmonary deterioration. We also based it on previous reports performed in patients with NPC2 [2, 8].

Progressive lung disease has been described in few NPC patients, mostly NPC2 patients [2, 7–9, 15, 23]. To the best of our knowledge, only a few NPC1 patients have been described with lung involvement, not secondary to recurrent aspiration. One description in the literature is of a 16-year-old patient with NPC1 disease. This patient had recurrent respiratory difficulties, persistent cough, and bronchial hypersecretion. Unlike our finding, "partial" bronchoalveolar lavage improved respiratory symptoms of the reported patient [16].

Roszell et al. have studied the NPC pathway in the lungs of mice and felines. By inhibiting the NPC pathway, they localized the NPC1 protein to the limiting membrane of the lamellar bodies and the NPC2 in the lumen of these organelles and also in the pulmonary lavage fluid [21, 22]. These findings may explain the improvement observed by Palmeri et al. in a patient with NPC1 after bronchoalveolar lavage [16] and it can also explain the development of interstitial lung disease in the more severe neonatal/infantile type of the disease compared to the more common adult type that shows mostly neurologic deterioration.

When comparing cholesterol accumulation in the lungs of NPC1 mice in comparison to wild-type mice, NPC1 mice had progressive accumulation of cholesterol in lungs with increased content of phospholipids in alveoli, as lipid-laden macrophages [19].

Accumulating foamy macrophages were demonstrated in our patient 3's lung biopsy and lavage as described in Table 2 and Fig. 2.

Our patients, coming from highly consanguineous Bedouins' families in Southern Israel, are homozygous for the p.R404Q mutation of the *NPC1* gene leading to a severe early infantile neurological form phenotype. It has been previously demonstrated by Meiner et al. that incubated fibroblasts from patients carrying this mutation on the *NPC1* gene had profoundly reduced cholesterol esterification (between 0 and 35 pmol CE/mg protein/6 h which is very low state % of normal activity) [13, 17].

Since part of the patients described so far as homozygous to p.*R404Q* mutation have an adult-onset neurological disease, this finding may only explain in part the severity of the disease. However, the unique pulmonary manifestations may be attributed to the specific p.*R404Q* mutation, located in the NPC2 protein-binding domain [4, 14]. The binding of NPC1 protein to a cholesterol-enriched NPC2 facilitates cholesterol transfer to the N-terminal domain of NPC1 protein, which is located at the lumen of late endosomes and lysosomes [4, 14]. Interference of NPC1 protein binding to NPC2 cholesterol-enriched protein, as expected in the p.*R404Q* mutation, would lead to cholesterol accumulation and pulmonary symptoms in a similar manner observed in patients with *NPC2* gene mutations [4].

A less likely explanation to the unique pulmonary phenotype in our patients is the presence of an additional common allele in other gene among our patients that causes pulmonary manifestations. However, we are not aware of any subjects with similar lung disease among healthy members (without NPC1) of these families.

It is conceivable that pulmonary deterioration in NPC1 patients is most probably a result of advanced lung infiltration by foamy macrophages and not due to recurrent aspirations.

Conclusion

We suggest that according to our patients' lung involvement and animal models, the pulmonary involvement is probably underestimated in NPC1 patients. Therefore, whenever there are pulmonary events in these patients, the possibility of primary lung pathology as part of the clinical spectrum of NPC1 disease should be considered.

Authors' contributions Orna Staretz Chacham was responsible for planning, conducting, and reporting of the study.

Micha Aviram and Iris Morag contributed for the conducting and reporting of the work.

Aviv Goldbart contributed for reporting of the study.

Eli Hershkovitz contributed for the planning and reporting of the study.

Compliance with ethical standards

This article does not contain any studies with human or animal subjects performed by the any of the authors; therefore, no informed consent was required. The study was approved by the Helsinki Committee of the institution.

Conflict of interest The authors declare that they have no conflict of interest.

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