Brief Communication

Anesthetic Consideration of Niemann-Pick Disease Type C

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Abstract

Niemann-Pick disease type C (NPC) is a rare, autosomal recessive, neurometabolic disorder associated with the accumulation of unesterified cholesterol in lysosomes and late endosomes. Because of multiple organ involvement and wide range of clinical manifestations, these patients will demand multiple diagnostic and therapeutic procedures requiring anesthesia. Since pathogenesis of this disease is still unknown and further investigations on cellular and molecular basis of NPC is needed. In this report we present a known case of NPC1 requiring anesthesia for Percutaneous Endoscopic Gastrostomy and a brief review about molecular basis and recent advances in this field.

Keywords: Anesthesia, Niemann-Pick Disease, Gene Mutation (NPC1); Intracellular Cholesterol Transport

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Introduction

Albert Niemann and Ludwig Pick in 1920's introduced an autosomal recessive disease characterized by disorders in liposomal lipid and sphyngomyeline storage, by common feature of hepatosplenomegaly with or without neurological involvements. Later in 1958 Crocker proposed a four group classification (A-D) based on age of onset, clinical implications and level of sphingomyelin storage in tissues (1, 2).

Type A defined by early CNS involvements and massive storage of visceral and cerebral sphingomyelin. Type B has a chronic course with visceral involvement and sparing CNS. Type C and D defined by sub-acute CNS involvement with milder visceral storage. Type D patients were individualized essentially on their homogenous Nova Scotia Acadian origin (1, 3).

Niemann-Pick Type C (NP-C), with a prevalence of 1/100000 – 1/120000, is characterized by progressive, disabling neurologic features (cerebellar ataxia, dysarthria, dysphagia, progressive dementia, cataplexy, seizures, dystonia and supranuclear gaze palsy) with mild visceral storages (liver, spleen, lungs) (1, 3). It is caused by mutations in either of two genes mentioned as NPC1 and NPC2.

NPC1 is involved in 95% of patients, including type D while NPC2 is present in certain families. These genes participate in cellular post lysosomal/late endosomal transport of cholesterol (4, 5). These changes result in sequestration of unesterified cholesterol in lysosomes and late endosomes (1, 2). Onset of NPC ranges from perinatal period till seventh decade of life, therefore life expectancy range from few days (Fetal hydrops) till over 60s; though majority of them die between 10 and 25 years from neurologic manifestations (1, 2).

Diagnosis of this disease is based on multidisciplinary process involving clinical assessments, histological, electron microscopic tests,

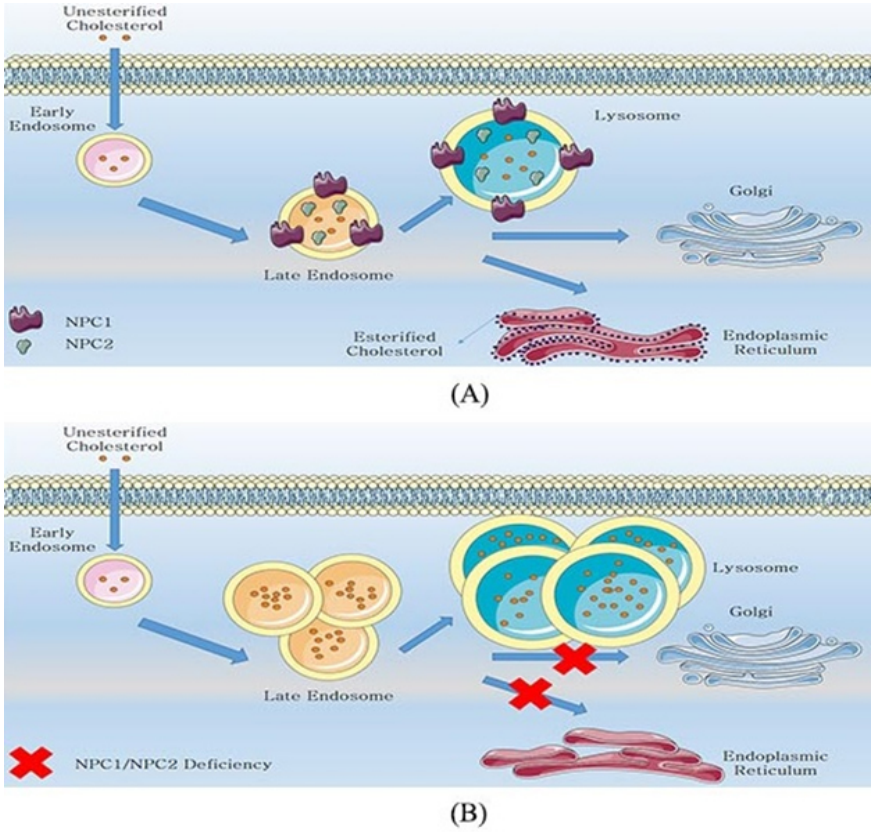

Fig. 1. (A) Normal esterification of cholesterol; (B) Esterification of cholesterol in NPC1/2**.**

biochemical, and molecular genetics laboratory studies (2). Final confirmation is based on demonstration of characteristics intralyposomal accumulation of unesterified cholesterol (Filipin staining in skin fibroblasts) and/or the identification of mutations in either the NPC1 or NPC2 genes (2). Novice areas of diagnosis are plasma oxysterols (particularly cholestane-3β,5α,6β-triol and 7-ketocholesterol), certain sphingolipids such as lysosphingosine (2).

Major clinical manifestations are dysphagia, recurrent aspirations leading to gastrostomy, severe epilepsy, severe hepatosplenomegaly and dramatic psychiatric disorders (1, 3, 6).

The only available approved therapy is Miglustat which could be prescribed as neurologic symptoms appeared. This drug can slower the progression of neurologic damage and also have some positive impacts on developing and progression of dysphagia (4, 6 7).

As discussed, the nature of the disease made it a target for diagnostic and therapeutic procedures that require anesthesia. This report will address anesthesia management of Niemann-Pick C and discuss cellular and molecular advances in this field.

Brief Report

A 9 years old boy, known case of Niemann-Pick C (NPC), was admitted to our hospital due to uncontrolled seizures and respiratory distress.

He was born at full term to nonconsanguineous parents by normal vaginal delivery without remarkable family history. His growth was normal in his first 6 months. Later on, splenomegaly observed and neurodevelopmental milestones were lost. Further examinations confirmed the diagnosis of NPC by cutaneous biopsy and Filipin staining. Since then Meglustat 100 mg TDS was initiated. He had developmental progression for the next 6 years till neurologic symptoms including seizures, ataxia, incontinency, and dysphagia emerged. His weekly seizures were managed by Lamotrigine, Sodium valproate and Prednisolone. Unfortunately respiratory symptoms (Productive cough, Wheezing) occurs from former month due to uncontrolled seizures, dysphagia

Table 1: Anesthetic consideration of Niemann-Pick Disease; *TV*, tidal volume, *RR*, respiratory rate, *FRC*, functional residual capacity, *TIVA*, total intravenous anesthesia.

Organ System	Associated Comorbidities	Anesthetic Consideration
Respiratory System	Restrictive Lung Disease	Lower TV and higher RR
	Recurrent Aspiration Pneumonia	
Gastrointestinal System	Hepatosplenomegaly	Decreased FRC and Increase in episodes of desaturation
	Ascites	
	Liver Failure	Consider Dosage Adjustments
	Sialorrhea	Anticholinergic as premedication could be beneficial
Airway	Difficult intubation	Consider anticipated difficult intubation algorithm
Hematologic System	Thrombocytopenia	Increased risk of bleeding
Central Nervous System	Seizure	Continue antiepileptic agents and avoid epileptogenic drugs
		Use of TIVA

and severe sialorrhea, suggesting aspirating pneumonia.

During his admission, antibiotics were prescribed. Antiepileptics changed to Topiramate and Levetiracetam. He was feeding through NG tube. After alleviation of respiratory symptoms and control of seizures, he was transferred for Percutaneous Endoscopic Gastrostomy.

On preoperative assessment, the patient weighed 40 Kg, the physical examination revealed bilateral rhonchi with increase in respiratory work. Baseline SpO2 was 94% in room air. Laboratory Data was within normal range.

Atropine 0.8mg/IV, Midazolam 1mg/IV and Fentanyl 50µg/IV was prescribed as premedication in endoscopic ward under full monitoring (ECG, Pulse oximetry, and NIBP). Induction was achieved by Propofol 80 mg/IV and the patient was intubated with ETT #5.0 under Direct Laryngoscopy. Infusion of Propofol was started for maintenance at 250 mg/hr. During procedure vital sign was stable and about 20 minutes after secession of maintenance the patient was extubated and transferred to ward.

Discussion

NPC is caused by mutations in one of the two genes called NPC1 or NPC2. 95% of cases have NPC1 mutation which encodes a large glycoprotein in late endosomal location. This gene mapped to chromosome 18q11-q12, spans 56 kbp and contains 25 exons. NPC2 encodes a small soluble lysosomal protein which binds cholesterol with high affinity (8). NPC2 mapped to chromosome 14q24.3, spans 13.5 Kbp and contains 5 exons. Deficiency in both types causes impairment in processing and utilization of endocytosed cholesterol (1, 8). The cellular hall mark of this disease is inability of cholesterol to transport from late endosomes to plasma membrane or reticulum endoplasmic therefore accumulation of cholesterol and products will occur (Figure 1) (1).

Therefore cholesterol storage is impeded and resulted in different pattern of accumulation in neuronal and extra-neuronal tissues. These changes cause sphingomyelin metabolism alteration in extra neuronal tissues. Unesterified cholesterol, sphingomyelin, bisphosphate, glycolipids, and free sphingosine and sphinganine will accumulate in liver and spleen(1). In neurons, accumulation of Glycosphingolipids including GM2 and GM3 gangliosides occurs and cause meganeurite formation, growth of ectopic dendrites, neurofibrillary tangles formation, neuroinflammation, and neuroaxonal dystrophy (8). On the other hand, some proteins like Rab9 or mannose-6-phosphate receptors transfer to cell membrane by late lysosomal system. Cholesterol accumulation could also impair this trafficking (1). Unexplainably neural death occurs mostly in Purkinje cells of the cerebellum. The function of these proteins are not defined yet so the exact mechanism and pathophysiology remains a mystery (1).

The only approved therapy for NPC so far is Miglustat (N-butyl-deoxynojirimycin). It is an iminosuger inhibitor of glucosylceramide synthase (1). This drug can stabilize the neurological manifestations including dysphagia (6). Miglustat by inhibiting glucosylceramide synthase reduce the synthesis of glucosylceramide-based glycosphingolipid in CNS (6). But long term clinical outcomes are still unclear (6). Other drugs used for symptom therapy including antiepileptic drugs (treatment of seizure), clomipramine, protriptyline, or modafinil (treatment of Cataplexy), anticholinergic agents (treatment of dystonia and tremor), Melotonin (treatment of insomnia). Physiotherapy for management of muscle spasticity and contracture is useful. As the major cause of mortality in these patients is aspiration pneumonia, the most important part of managing this disease is handling feeding abnormalities (1, 6). Current researches in the field of treating this disease is based on animal models mostly transgenic mice and cats and also testing various compounds like imatinib, curcumin, NSAIDs, neurosteroids (allopregnolone) and 2-HP-ß-cyclodextrin. The last compound showed significant improvement in disease natural history in animal models but needs further investigations (1).

The exact function of NPC genes are unknown therefore the pathophysiology of this disease is still a mystery (4). So the target metabolite in brain causing the neuroinflammatory responses remains unknown. These results are in lack of a biochemical blood test for evaluating prognosis or diagnosis (1, 4). Currently the gold standard for diagnosis is skin biopsy however recent advances suggest oxysterol profile as a biomarker for NPC. Although more researches are needed to define it as an indicator, these findings could change the future treatment and research developments (1, 4).

As mentioned above, NPC is a disease which involves multiple organs including central nervous system, respiratory system and gastrointestinal system (hepatosplenomegaly). Therefore this disease could interfere with routine anesthetic plans (3, 5). Restrictive lung disease arise from recurrent aspirations demand specific consideration in ventilator setup, so lower tidal volumes and increase in respiratory rate could be helpful for these patients. Another problem is the liver damage caused by storage of lipids, which needs careful selection of anesthetic drugs (5). Also hepatomegaly could accompany ascites which leads to decreased Functional Residual Capacity (3). there are some reports indicating the association between NPC and difficult airway therefore considering options for intubation would be wise (1). on the other hand, thrombocytopenia accompanied by this disease, could potentiate the risk of bleeding (1). Due to vigorous

secretions anticholinergic drugs prior to anesthesia could improve the outcome of the procedure (3). It is demonstrated that hyperventilation plus high concentrations of Sevoflurane could induce seizures. Therefore to avoid this phenomenon continuing antiepileptic agents in perioperative period and use of TIVA instead of volatiles is recommended (3). The technique of choice is the one in which satisfactory condition for procedure is established rapidly and safely and also the recovery should be safe and predicted with minimal sequel for the patient (5).

Conclusion

Although almost a century has passed since the introduction of NPC, there are many unknown aspects which could be a good target for future researches. These unrevealed areas of investigations include absence of biomarker for evaluating treatments, exact pathophysiology, and introduction of effective treatment. Diversity of clinical manifestations together with unknown pathophysiology results in the complexity and enigmatic features of this disease.

Some of manifestations of NPC can affect the anesthetic plan. These comorbidities are summarized in table 1. In conclusion by considering comorbidities and anesthetic implications mentioned above and severity and type of procedure or surgery, each patient with different clinical symptoms could benefit from different anesthetic approaches (1, 5).

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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