- Increased off-label use of antipsychotics
- Differentiating NMS from serotonin syndrome, malignant hyperthermia, drug-induced extrapyramidal reactions, and substance-abuse withdrawal

Overview

- Rare, iatrogenic hypermetabolic reaction characterized by fulminant or insidious development of muscular rigidity, altered sensorium, dysautonomia, and high fever.
- Triggered by antidopaminergic agents or DA agonist withdrawal.
- More common in pts with psychiatric Hx of schizophrenia, schizoaffective disorder, bipolar disorder, mental retardation, Parkinson disease, dementia, and psychosis.
- Despite declining frequency likely due to more widespread recognition and earlier diagnosis/treatment, NMS remains a significant source of morbidity and mortality for pts taking antipsychotics.
- Shares striking clinical similarities with but is otherwise pathophysiologically distinct from malignant hyperthermia; to date, no definitive evidence demonstrating that NMS increases the risk of malignant hyperthermia under general anesthesia.

Etiology

- Central D_2 receptor antagonism triggers a cascade of disrupted DA receptor–mediated signaling pathways with resultant autonomic dysregulation and end stage hypermetabolic syndrome.
- Known triggering scenarios include DA antagonists, DA-agonist withdrawal, and GABA-agonist withdrawal.

- Once NMS is diagnosed and the triggering agent discontinued, NMS is generally self-limited, and full resolution can be expected to occur within 1 wk to 10 d, with appropriate supportive therapy.

Usual Treatment

- Dx of exclusion; rule out alternate causes of symptoms.
- Immediate discontinuation of triggering medication.
- Consider use of benzodiazepines, dantrolene, DA agonists, or electroconvulsive therapy.
- Supportive care including airway protection, hemodynamic stabilization, temperature regulation, fluid resuscitation, and lyte correction as indicated.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Dystonia	Increased facial tone with involuntary contractions Excess saliva	Oculogyric crisis, trismus, blepharospasm, dysarthria, and dysphagia Sialorrhea Facial flushing	
RESP	Pulm aspiration Hypoxemia Acute pulm edema Pulm embolus	Respiratory distress Dyspnea	Lung-field consolidation Tachypnea	CXR and CT scan ABG Bronchoalveolar lavage V/Q scan
CV	Dysautonomia Reversible dilated cardiomyopathy	Diaphoresis, chest pain, dyspnea, and palpitations	Tachydysrhythmias and labile BP	ECG, ECHO, and coronary angiogram
CNS	Delirium Hyperthermia Extrapyramidal symptoms Metabolic encephalopathy	Disorientation Fever	Altered mental status and agitation Choreiform/dyskinesia	CT/MRI CSF analysis and EEG
RENAL	Myoglobinuria Acute kidney failure Metabolic acidosis	Dark-red urine	Oliguria	Electrolytes, UA, BUN, and Cr
HEME	Leukocytosis DIC			CBC Fibrinogen and coagulation

Key References: Strawn JR, Keck PE Jr, Caroff SN: Neuroleptic malignant syndrome, *Am J Psychiatry* 164(6):870–876, 2007; Mustafa HI, Fessel JP, Barwise J, et al.: Dysautonomia: perioperative implications, *Anesthesiology* 116(1):205–215, 2012.

Perioperative Implications

Preoperative Preparation

- Conduct a thorough review of home medications/inpatient regimen with particular attention to antipsychotics and confirmation of date/time of last dose.
- If concern exists for active NMS, postpone any elective procedure until pt is clinically stable.

Monitoring

- Arterial line if indicated
- Urine output for myoglobinuria

Airway

- Anticipate copious secretions w/ possible dysphagia and muscular rigidity in pts with active NMS.
- Consider full stomach precautions.

Preinduction/Induction

- Pt may exhibit exaggerated hemodynamic response to induction medications and volatile agents.

Maintenance

- Vigilant management of blood pressure and volume status
- Neuromuscular blockade to reverse severe muscular rigidity if indicated
- Diuresis

Extubation

- Keep intubated if concern for airway protection exists.

Postoperative Period

- May require a higher level of care

Anticipated Problems/Concerns

- Periop autonomic dysfunction
- Increased risk for aspiration and periop pulm complications
- Clinical presentation similar to malignant hyperthermia but with no pharmacologic crossover

Niemann-Pick Disease

Thomas Schilling | Alf Kozian

Risk

- Incidence in live births: 1:100,000-120,000
- Affects equally males and females of all ethnic groups
- NP-D type A frequent in the Ashkenazi-Jewish population
- No curative therapy, although several symptomatic manifestations are treatable
- Associated with a decrease in life expectancy, although many pts survive until late adulthood

Perioperative Risks

- NP-D pts require a multitude of diagnostic and therapeutic procedures (e.g., medical imaging, lumbar puncture, intrathecal chemotherapy injection, auditory brainstem response measurements, and skin biopsies). General anesthesia with endotracheal intubation is often required.
- Pts at increased risk of aspiration, especially those with severe lung involvement, recurrent aspiration, and chronic cough.
- Perianesthetic morbidity includes need for tracheal reintubation; pneumonitis, hypothermia, and seizures.

Worry About

- Severe visceral, pulmonary, and neurologic involvement
- Hepatomegaly, ascites, coagulation disorders, and hypersplenism with thrombocytopenia

- Alterations of liver function and in some cases, liver cirrhosis and liver failure
- Rarely causes spontaneous splenic rupture
- Recurrent respiratory infections are common; prior episodes of aspiration

Overview

- It is classified into the neurovisceral lysosomal lipid-storage disease group (types A–D).
- Two distinct entities exist: acid sphingomyelinase deficiency (type A and B) and loss-of-function mutations in either the *NPC1* or *NPC2* genes (C and D).
- Age of clinical onset varies widely.
- Broad clinical spectrum ranges from a rapidly fatal disorder in neonates to an adult onset chronic neurodegenerative disease, a mix of visceral and neurologic deficits including vertical gaze palsy, ataxia, dystonia, dysphagia, seizures, and progressive dementia.
- With systemic disease, hepatosplenomegaly can be severe.
- Lung involvement can be present and results from severe neurologic impairment and associated dysphagia, recurrent aspirations, and thoracic muscle weakness.

Etiology

- Autosomal recessive lysosomal storage disorders
- Mutations in the *SMPD1* gene (types A and B) resulting in sphingomyelinase deficiency with progressive accumulation of sphingomyelin in systemic organs and brain, and secondary accumulation of other lipids
- Historically, categorized into a severe, acute neuronopathic form (A), and a nonneuronopathic form (B), also intermediate cases
- Extremely variable degree of systemic involvement depending on age of discovery; retarded body growth (common); often delayed skeletal age and puberty
- Vomiting and diarrhea in first months of life; failure to thrive often motivating a first consultation, leading to the discovery of a usually prominent hepatosplenomegaly (80% of pts); additionally, hypotrophy, dysmorphia, brownish skin pigmentation, macular halo, and cherry-red spots, which are typical
- Further hypotonia, progressive loss of acquired motor skills, increasing spasticity, abolished deep-tendon reflexes, joint/limb pain, bruising, headache, abdominal pain, and diarrhea
- NP-D type C, which involves alterations in the intracellular transport of endocytosed cholesterol and accumulation of unesterified cholesterol in lysosomes and endosomes due to mutations in either the *NPC1* (95% of families) or *NPC2* genes
- Hypercholesterolemia with marked decrease of HDL cholesterol (common); complex lipid storage observed in extra neural tissues
- Pulmonary involvement:
  - Common at all ages, with widely variable impairment of respiratory function ranging from dyspnea on exertion (frequent) to oxygen dependency
  - CXR: Reticulonodular pattern, interlobular septal thickening, ground-glass density; in adults with a long follow-up, pulm involvement (often the main complaint)

Usual Treatment

- Management remains largely symptomatic.
- Gastrostomy is often required.
- Splenectomy is seldom necessary and should be avoided.
- Pts who progress to liver failure require liver transplantation.
- Neurologic manifestations of NP-D C: Miglustat; cataplexy often responds to protriptyline, clomipramine, or modafinil.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Airway difficulties Intubation problems Aspiration	Dyspnea	Barrel chest, very short neck Neck mobility diminished Degeneration of the cervical vertebral column Mental–zygomatic distance reduced Muscle contractures, extensive degeneration of bone, joint in the vertebral column	Mallampati score (limited)Thyromental distance Neck mobility
CV	Reduction of overall left ventricular function Poor diastolic function by lipid storage CAD Pulm arteriovenous fistulas Pulm Htn	Poor exercise tolerance Angina pectoris CHF symptoms	Two-flight walk 6-min walking test	ECG CXR ECHO Cath coronary angiography Spiroergometry
RESP	Decrease in lung volume and FRC Interstitial lung disease Lipoid pneumonia Recurrent aspiration Hypoxemia	Cyanosis, clubbing, fine crackles Recurrent lung infections Dyspnea (increasing breathlessness) Chronic cough Respiratory failure	Inspection, auscultation	Chest x-ray Body plethysmography Lung biopsy High-resolution CT Flexible bronchoscopy Broncho-alveolar lavage
HEPAT/GI	Hepatomegaly, liver damage Drop in hepatic blood flow Changes in drug metabolism Coagulopathy Hepatopulmonary syndrome Splenomegaly Neonatal cholestatic jaundice	Dysphagia Ascites Gastroparesis Anterior abdominal wall elevation	Inspection, palpation	US scan of the abdomen Liver enzymes Thrombocyte count and function Routine lab tests often not helpful
RENAL/ENDO	Nothing specifically known			
CNS	Neurodegeneration Progressive dementia	Transient consciousness Vertical supranuclear gaze palsy Seizure Cerebellar ataxia Dystonia, dysphagia	Neurologic/mental status Cognitive function tests	EEG Brain MRI Auditory brainstem potential Lumbar puncture Psychometric assessment
PNS	Progressive damage to the PNS with demyelization	Motor pathologies Horizontal saccadic eye movements Speech difficulties Cataplexy	PNS examination	Clinical exams: HSEM, cognition, ambulation, swallowing, hearing deficit, and speech delay Muscle tone and strength tests, motor reflexes, assessment of movement, and swallowing testing
MS	Anatomic disorders	Generalized developmental disturbances		

Key References: Patterson MC, Hendriksz CJ, Walterfang M, et al.: Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update, *Mol Genet Metab* 106(3):330–344, 2012; Miao N, Lu X, O'Grady NP, et al.: Niemann-Pick disease type C: implications for sedation and anesthesia for diagnostic procedures., *J Child Neurol* 27(12):1541–1546, 2012.

Perioperative Management

Preoperative Preparation

- Assess extent of visceral and neurologic involvement, as well as the cardiac and volume status.
- Check liver enzymes, lipids, and respiratory function, as well as the coagulation status and function of thrombocytes.
- Pt with severe lung disease, recurrent aspiration, and chronic cough at risk of aspiration; consider antacid therapy.
- Check for possible regional anesthesia.
- Majority are ASA class III.
- Maintain anticonvulsants.

Monitoring

- Airway and oxygen saturation
- Noninvasive blood pressure

- ECG: Myocardial ischemia; possible CHF if volume overload and LV dysfunction is present
- Temperature monitoring

Induction

- Consider rapid sequence induction.
- Swallowing secretions: Consider anticholinergic agents.
- Cave hypovolemia; CV dysfunction makes BP and HR fluctuate.

Maintenance

- Inhalational anesthetics (sevoflurane and nitrous oxide) and sedatives (midazolam and propofol) were used.
- >2.0 MAC sevoflurane and hyperventilation can be associated with epileptiform activity on EEG.

Extubation

- CV and pulm-drive insufficiencies (common with neuropathies)
- Aspiration risk

Adjuvants

- Regional/neuraxial anesthesia possible despite neurodegeneration

Postoperative Period

- Possible tracheal reintubation, hypothermia, and seizure
- Can keep pt in ICU/PACU overnight

Anticipated Problems/Concerns

- Increased intraabdominal pressure and decreased FRC
- Decreases in oxygen saturation
- Hypothermia
- Gastroparesis

Noonan Syndrome

Jiri Horak | Alexander Fort | Lee A. Fleisher

Risk

- Incidence between 1:1000-2500 live births
- Incidence consistent worldwide
- Equal distribution between genders

Perioperative Risks

- Airway
- Cardiovascular
- Hematologic
- Infectious

Worry About

- Difficult airway
- Cardiovascular complications
- Bleeding
- Endocarditis

Overview

- Key features include facial anomalies, neck webbing, short stature, chest deformity, spinal deformity (e.g., scoliosis, atlanto-occipital fusion, cervical fusion), congenital heart disease (e.g., pulmonic stenosis, hypertrophic obstructive cardiomyopathy), bleeding diathesis, mental retardation.
- Congenital heart disease may include pulmonic stenosis (in 80% of cases); hypertrophic obstructive cardiomyopathy (20–30%). Less common lesions include ventricular septal defect, tetralogy of Fallot, aortic stenosis, coarctation of the aorta, Ebstein malformation, total anomalous pulm venous return, and patent ductus arteriosus.
- Increased incidence of cancers, especially hematologic, with roughly a 3.5-fold increased risk.

Etiology

- Primarily an autosomal dominant disorder; however, sporadic cases are reported.
- Mutation on the PTPN11 gene on chromosome 12 in roughly 50% of cases.
- Also associated with mutations in genes that are part of the RAS/RAF/MEK/ERK signal transduction pathway (regulators of cell growth).

Usual Treatment

- Repair congenital cardiac defects.
- Administer growth hormone.
- Treat hematologic disorders.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Facial deformity Atlanto-occipital or cervical instability or fusion	Instability Pain	Limited neck range of motion	Cervical spine x-ray
RESP	Chest wall deformity Restrictive lung disease Pulm edema	Dyspnea	Tachypnea Crackles	CXR CT scan PFTs ABG
CV	Congenital heart disease (repaired or unrepaired, most commonly HOCM or PS)	Dyspnea Orthopnea Exercise intolerance Syncope Arrhythmias	Tachycardia Murmur S_3/S_4 Displaced PMI JVD	ECG ECHO Cardiac cath
GI	Hepatic congestion Hepatosplenomegaly Decreased appetite Gastroparesis	Abd pain N/V Failure to thrive Weight loss	RUQ tenderness/fullness Jaundice	LFTs RUQ US Albumin/prealbumin
ENDO	Growth hormone supplementation	Glucose intolerance Hypertension Dyslipidemia		BMP Lipid profile
CNS	Mental retardation Seizures	Developmental delay		Mental status exam
HEME	Bleeding disorder Hematologic malignancy	Easing bruising Epistaxis Bleeding gingiva GI bleed Fatigue	Pallor Petechiae Hematochezia Melena	CBC with differential Coagulation profile Bleeding time Fibrinogen vWF Factor levels
MS	Scoliosis Joint laxity	Restrictive lung disease	Spinal curvature	Lumbar/thoracic spine x-ray PFTs
METAB	Lyte abnormalities from zmalnutrition	Fatigue Weight loss ECG changes		BMP/Mg/Ph ECG

Key Reference: Aggarwal V, Malik V, Kapoor PM, et al.: Noonan syndrome: an anesthesiologist's perspective, *Ann Card Anaesth* 14(3):214–217, 2011.