orphanesthesia

Anesthesia recommendations for

Infantile Neuroaxonal Dystrophy

Disease name: Infantile neuroaxonal dystrophy

ICD 10: G23.0, G71.09, G31.8

ICD 11: 5C64.10

ORPHAcode: 35069

Synonyms: PLA2G6-related neurodegeneration, INAD, Neurodegeneration with Brain Iron Accumulation type 2 (NBIA2), Phospholipase A2-associated neurodegeneration (PLAN)

Brief disease summary: Infantile neuroaxonal dystrophy (INAD) is the childhood manifestation of PLA2G6-associated neurodegeneration (PLAN), a continuum of phenotypes from infancy to adulthood. PLAN is inherited in an autosomal recessive fashion [1]. Disease prevalence is estimated to be between 1:987,267 and 1:1,570,079 pregnancies worldwide [2]. There are four PLAN phenotypes: classic INAD, atypical neuroaxonal dystrophy, early-onset dystonia-parkinsonism and later onset phenotypes.

Infantile PLAN usually presents between ages six months and three years with truncal hypotonia, psychomotor delay and plateauing loss of previously acquired milestones. Over time, weakness and symmetric spastic tetraparesis develop, resulting in discomfort, interference with bracing or positioning, and leading to contractures and neuromuscular scoliosis. Limb dystonia can also be present. Strabismus, nystagmus, and optic atrophy are common. Many infantile PLAN patients also experience progressive dementia. Bulbar dysfunction is a common cause of respiratory complications [3]. Infantile PLAN is a severe neurodegenerative disorder with a life expectancy of 5 to 10 years [4,5]. Treatment is supportive and focuses on managing symptoms [6]. Medical care typically consists of a multidisciplinary team of educators for developmental delay and intellectual disability, a neurologist for anti-seizure medications and pharmacologic treatment of dystonia and spasticity, psychiatric treatment for those with later-onset neuropsychiatric manifestations, fiber supplements and/or stool softeners for constipation, control of secretions with transdermal scopolamine and feeding modifications as needed to prevent aspiration pneumonia and achieve adequate nutrition. The main anesthetic concern for INAD patients is their impaired preoperative respiratory status due to poor airway clearance and respiratory mechanics that often makes postoperative intubation necessary [7].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.



Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.



Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

A	**AIRWAY / ANESTHETIC TECHNIQUE**	Difficult mask ventilation and tracheal intubation can occur due to cervical contractures, limited cervical spine mobility, temporomandibular joint restriction, reduced mouth opening, trismus, and torticollis, which may persist despite neuromuscular blockade. Bulbar dysfunction, impaired airway reflexes, excessive secretions, and diminished cough increase the risk of aspiration and perioperative respiratory complications. Some patients may have a pre-existing tracheostomy. Airway management should anticipate both difficult ventilation and difficult intubation. Videolaryngoscopy should be immediately available, with suction readily accessible to manage excessive secretions. Tracheostomy equipment should be present when appropriate, particularly in patients with established tracheostomies or severe airway compromise. Induction and emergence strategies should be individualized. Rapid sequence induction may be beneficial when aspiration risk is substantial. Extubation should generally be performed when patients are awake and have demonstrated adequate airway protective reflexes. Postoperative noninvasive respiratory support should be considered in children with significant bulbar dysfunction, respiratory muscle weakness, or a history of nocturnal ventilatory assistance.
B	**BLOOD PRODUCTS (COAGULATION)**	There are no disease-specific hematologic abnormalities or transfusion requirements. The principal transfusion consideration relates to the procedures these patients commonly undergo.
C	**CIRCULATION**	Preoperative ECG and echocardiogram should be considered as patients with advanced disease may develop pulmonary hypertension and right ventricular failure.
D	**DRUGS**	Sedative premedication should be used cautiously because of limited respiratory reserve and susceptibility to hypoventilation. Inhalation anesthetics, propofol, and opioids have been used safely, and there is no evidence of an association with malignant hyperthermia or anesthesia-associated rhabdomyolysis.

		Succinylcholine should be avoided because chronic immobilization and denervation may predispose patients to hyperkalemic cardiac arrest. Antispasticity medications (e.g., baclofen, benzodiazepines) may potentiate sedation and respiratory depression. Concurrent anticonvulsant therapy may alter the metabolism of anesthetic agents. Dopaminergic antagonists (e.g., metoclopramide, phenothiazines, and butyrophenones) may exacerbate movement disorders.
E	**EQUIPMENT**	Quantitative neuromuscular monitoring should be employed whenever neuromuscular blocking agents are administered. Postoperative noninvasive respiratory support should be considered in children with significant bulbar dysfunction, respiratory muscle weakness, or a history of nocturnal ventilatory assistance. Transportation within the operating suite and to the postoperative care area should include appropriate respiratory monitoring, as patients may have limited pulmonary reserve, impaired secretion clearance, and an increased risk of hypoventilation. Children receiving chronic noninvasive ventilation or airway clearance therapies should have these modalities readily available during postoperative transfer.

Additional disease information

PLAN is the second most common type of neurodegeneration with brain iron accumulation after pantothenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden-Spatz disease). PLA2G6 encodes a calcium-independent phospholipase, which is expressed in and protective of mitochondrial health and is also important for membrane homeostasis and calcium signaling. INAD is characterized histologically by axonal spheroid bodies [3].

Typical surgery and procedures

Surgical procedures typically consist of gastrostomy tube placement and revisions, tracheostomy, orthopedic procedures including scoliosis surgery, dental rehabilitation, deep brain stimulation procedures, imaging under anesthesia such as repeated diagnostic imaging or MRI, central venous access procedures, and botulinum toxin injections for focal dystonia or spasticity.

Type of anesthesia

Cautious use of premedication because of respiratory compromise.

General anesthesia is usually well tolerated when appropriate attention is paid to respiratory reserve and airway protection [7].

There is no evidence that volatile anesthetics precipitate malignant hyperthermia or anesthesia-induced rhabdomyolysis in PLAN.

Succinylcholine should be avoided because of prolonged immobility, severe neuromuscular weakness, and the risk of hyperkalemia [7].

Neuromuscular blocking agents should be used when clinically necessary.

Quantitative neuromuscular monitoring should be employed whenever neuromuscular blocking agents are administered.

Patients may demonstrate increased sensitivity and prolonged recovery following nondepolarizing neuromuscular blockade.

Sugammadex is now available for rapid reversal of aminosteroidal neuromuscular blocking agents, and its widespread pediatric use has significantly altered practice [8].

Necessary additional preoperative testing (beside standard care)

Evaluate for:
- Chronic aspiration
- Recurrent pneumonias
- Ineffective cough
- Secretion burden
- Nocturnal hypoventilation
- Home BiPAP or CPAP use
- Tracheostomy dependence
- Baseline oxygen requirements

Additional investigations when indicated:
- Chest radiography
- Capnography
- Venous or arterial blood gases
- Sleep studies if available
- Pulmonary function testing if patient is able to cooperate
- Pulmonary consultation

Specific considerations for cardiovascular evaluation:
- Preoperative electrocardiogram and echocardiogram should be considered, as patients with advanced disease may develop pulmonary hypertension and right ventricular dysfunction.

Specific considerations for neurologic evaluation:

- Seizure frequency
- Anticonvulsant therapy
- Dystonia
- Spasticity
- Developmental status
- Communication abilities

Particular preparation for airway management

Patients with PLAN may present significant airway challenges [7].

Difficult mask ventilation and tracheal intubation can occur due to cervical contractures, limited cervical spine mobility, temporomandibular joint restriction, reduced mouth opening, trismus, and torticollis, which may persist despite neuromuscular blockade.

Bulbar dysfunction, impaired airway reflexes, excessive secretions, and diminished cough increase the risk of aspiration and perioperative respiratory complications.

Some patients may have a pre-existing tracheostomy.

Airway management should anticipate both difficult ventilation and difficult intubation. Videolaryngoscopy should be immediately available, with suction readily accessible to manage excessive secretions.

Tracheostomy equipment should be present when appropriate, particularly in patients with established tracheostomies or severe airway compromise.

Induction and emergence strategies should be individualized. Rapid sequence induction may be beneficial when aspiration risk is substantial. Extubation should generally be performed when patients are awake and have demonstrated adequate airway protective reflexes.

Postoperative noninvasive respiratory support should be considered in children with significant bulbar dysfunction, respiratory muscle weakness, or a history of nocturnal ventilatory assistance.

Particular preparation for transfusion or administration of blood products

There are no disease-specific hematologic abnormalities or transfusion requirements described in INAD. The principal transfusion consideration in INAD relates to the procedures these patients commonly undergo. Children presenting for scoliosis correction, in particular, may experience substantially greater intraoperative blood loss than patients with idiopathic scoliosis. Blood conservation strategies for high-blood-loss procedures such as tranexamic acid, meticulous surgical hemostasis, and autologous cell salvage should be used when available and appropriate. Invasive monitoring such as arterial catheterization should be considered for major procedures to facilitate serial blood gas and hemoglobin assessment.

Particular preparation for anticoagulation

No disease-specific anticoagulation abnormalities have been reported in INAD, and there are no published recommendations for routine perioperative anticoagulation or alterations in standard anticoagulant management. Anticoagulation management should therefore follow standard pediatric perioperative guidelines and be individualized according to the patient's thrombotic risk, the surgical procedure, and the planned anesthetic technique.

Particular precautions for positioning, transportation and mobilization

Patients with advanced INAD frequently develop spastic tetraplegia, severe weakness, contractures, scoliosis, optic atrophy, and impaired respiratory function [3], necessitating meticulous attention during perioperative positioning and transport. Care should be taken to prevent pressure injury, peripheral nerve compression, joint dislocation, and exacerbation of existing musculoskeletal deformities. Particular attention should be paid to cervical alignment in patients with cervical contractures and to padding of pressure points during prolonged procedures.

Transportation within the operating suite and to the postoperative care area should include appropriate respiratory monitoring, as patients may have limited pulmonary reserve, impaired secretion clearance, and an increased risk of hypoventilation. Children receiving chronic noninvasive ventilation or airway clearance therapies should have these modalities readily available during perioperative transfer.

Interactions of chronic disease and anesthesia medications

While there are no known disease-specific pharmacodynamic interactions between INAD and commonly used anesthetic agents, several clinically important considerations arise from the underlying neuromuscular and neurologic manifestations of the disease.

Antispasticity medications (e.g., baclofen, benzodiazepines) may potentiate sedation and respiratory depression.

Concurrent anticonvulsant therapy may alter the metabolism of anesthetic agents.

Dopaminergic antagonists (e.g., metoclopramide, phenothiazines, and butyrophenones) may exacerbate movement disorders.

Anesthetic procedure

See above.

Particular or additional monitoring

See above, especially monitoring of neuromuscular function.

Possible complications

Respiratory:
- Aspiration pneumonitis
- Postoperative hypoventilation
- Secretion retention
- Failed extubation
- Atelectasis

Neurologic:
- Seizures
- Prolonged sedation
- Dystonic crises

Musculoskeletal:
- Pressure injuries
- Positioning injuries

Cardiopulmonary:
- Pulmonary hypertension
- Right heart dysfunction

Postoperative care

Respiratory support – patients may require:

- Prolonged postoperative ventilation
- BiPAP or CPAP
- Aggressive pulmonary toilet
- Mechanical cough assistance
- Chest physiotherapy

ICU admission – consider ICU admission for:

- Major surgery
- Pre-existing respiratory insufficiency
- Home ventilatory support
- Tracheostomy dependence
- Severe bulbar dysfunction

Disease-related acute problems and effect on anesthesia and recovery

Patients may have severe weakness which may be confused with residual neuromuscular blockade if a non-depolarizing neuromuscular blocking agent has been administered.

Ambulatory anesthesia

Most patients with classic INAD are poor candidates for ambulatory anesthesia because of respiratory compromise and postoperative monitoring requirements. Selected patients with milder PLAN phenotypes undergoing minor procedures may be appropriate candidates after multidisciplinary assessment with a plan for hospital admission if needed.

Obstetrical anesthesia

Patients with classic INAD generally have an extremely short life expectancy (less than 10 years of age) and are unlikely to reach childbearing age.

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Please note that this recommendation has not been reviewed by an anesthesiologist and a disease expert but by two anesthesiologists instead.

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