

# Visceral Hyperalgesia: When to Consider Gabapentin Use in Neonates—Case Study and Review

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## Abstract

Visceral hyperalgesia refers to increased pain sensation in response to gastrointestinal sensory stimulus. In neonates with neurological impairments, gabapentin has been successfully used as a treatment for visceral hyperalgesia in neonates. The authors describe a preterm infant with myelomeningocele and persistent neuropathic pain that manifested as irritability, hypertonicity, poor weight gain, and feeding intolerance. After exclusion of other etiologies, the diagnosis of visceral hyperalgesia was suspected and the infant was treated with gabapentin. Following appropriate titration to effect and close monitoring of side effects of gabapentin, he subsequently demonstrated improved tone, decreased irritability with feedings, and appropriate weight gain. In addition, the authors provide a review of the available literature of gabapentin use in neonates and offer suggestions on when to consider starting gabapentin in a neonate with neurological impairment and chronic unexplained gastrointestinal manifestations.

## Keywords

gabapentin, visceral hyperalgesia, neonates, neuropathic pain

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Visceral hyperalgesia refers to increased pain sensation in response to gastrointestinal sensory stimulus.<sup>1-3</sup> In neonates with neurological impairments, visceral hyperalgesia has been described as an underlying source of neuropathic pain that manifests as irritability, hypertonicity, poor weight gain, and feeding intolerance, all common neurological and gastrointestinal symptoms of prematurity.<sup>2-6</sup> Visceral hyperalgesia is often misdiagnosed or not even considered as an etiology.<sup>7</sup> There are only a few case reports and case series that describe visceral hyperalgesia in neonates and its causes, diagnosis, and treatment options.<sup>1-6</sup> These same case reports describe the successful use of gabapentin as a treatment for visceral hyperalgesia in neonates. The mechanism of action of gabapentin, a  $\gamma$ -aminobutyric acid analog, is thought to inhibit pain via voltage-dependent calcium ion channels in the central nervous system and relieve the neuropathic pain in response to the gastrointestinal stimulus.<sup>7-10</sup>

In this case report, the authors present a preterm infant with a myelomeningocele treated with gabapentin for visceral hyperalgesia that manifested with irritability, hypertonicity, poor weight gain, and feeding intolerance. The authors also provide a review of the available literature of gabapentin use in neonates and offer specific recommendations on when to

consider visceral hyperalgesia and start gabapentin in neonates with neurological impairment and chronic unexplained gastrointestinal manifestations. The institutional review board at Atlantic Health System approved the study.

## Case Report

Our patient is a male infant born via cesarean section at 29 weeks' gestational age to a 24-year-old mother for worsening

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preeclampsia. The infant's birth weight was 995 g (20th percentile) and head circumference was 25 cm (10th percentile). The initial physical examination revealed a 1 cm × 1 cm neural tube defect in the lumbosacral area consistent with a myelomeningocele that was not detected prenatally. He underwent primary closure of the defect at 1 week of life. The initial and subsequent head ultrasounds did not identify hydrocephalous, intraventricular hemorrhage, or Chiari II malformation. The head circumference grew along the 10th percentile throughout his hospital course. He had normal, symmetric movement of his 4 extremities with increased tone and normal urination and stooling patterns. He had no sensory deficits noted on the dermatomal evaluation of the lower extremities, especially in the sacral region, before or after repair. He passed the auditory brain stem response-hearing screen and had no retinopathy of prematurity.

The infant had poor weight gain (<15 g/d from birth to day of life 100), extreme irritability, hypertonicity, and significant feeding intolerance (vomiting and arching with feeds) that was out of proportion for prematurity. At 42 weeks postmenstrual age, he was still requiring feedings via a nasogastric tube. The diagnostic workup for his gastrointestinal and neurological manifestations of pain and irritability, including brain and spine magnetic resonance imaging, and modified barium/follow through speech evaluation did not reveal any pathology.

At 43 weeks postmenstrual age, with no identifiable source for the irritability and feeding intolerance, manifested as poor oral intake and lack of weight gain, a diagnosis of visceral hyperalgesia was considered and the infant was trialed on gabapentin. The dose was titrated to effect by administering gabapentin at 5 mg/kg/d by mouth at night on days 1 and 2, 10 mg/kg/d divided twice daily on days 3 and 4, and 15 mg/kg/d divided 3 times daily from day 5 onward. The regimen was adopted from the previous literature, and gabapentin was initially administered via the nasogastric tube.<sup>1,4</sup> His nasogastric tube was removed after 3 days of starting the medicine, at which time the medicine was switched to oral administration, and he gained an average of 28 g/d until his discharge at 46 weeks postmenstrual age. His tone improved and irritability dissipated. He was discharged home on gabapentin, and the dose and interval were slowly weaned over 3 months by his pediatric neurologist. Adverse clinical events associated with initiation, maintenance, and discontinuation of gabapentin were closely monitored but never experienced by this patient (Table 1).<sup>1,3,4,10,11</sup>

## Discussion

In this case study, the authors present a neurologically impaired preterm infant with a repaired myelomeningocele who was successfully treated with gabapentin for visceral hyperalgesia. The diagnosis and treatment options for neonates with neurological impairments and persistent irritability due to visceral hyperalgesia are an underreported topic in the literature. The challenge of identifying symptoms of neuropathic pain and distinguishing them from common neonatal morbidities makes

**Table 1.** Adverse Experiences of Gabapentin Use.

Phase	Adverse Events
Initiation	GI intolerance <sup>10</sup> Oversedation <sup>10</sup> Bradycardia <sup>3</sup>
Maintenance	Nystagmus <sup>1,4,10</sup> Somnolence, fatigue <sup>10</sup> Ataxia/dizziness <sup>10</sup> Nausea/vomiting <sup>10</sup>
Discontinuation	Autonomic instability <sup>10,11</sup> Tachycardia <sup>3</sup> Emesis Agitation <sup>3</sup>

Abbreviation: GI, gastrointestinal.

the task of adequately treating more difficult. In patients with severe neurologic impairment (ie, intraventricular hemorrhage, periventricular leukomalacia, cystic encephalomalacia, ventriculoperitoneal shunt, myelomeningocele, etc), gastroesophageal reflux, constipation, feeding difficulties and poor weight gain due to poor gut motility, spasticity, and pain have all been described as potential manifestations of visceral hyperalgesia (Table 2).<sup>7</sup> Often, there is a reliance on nasogastric or gastrostomy tube.<sup>3,4,6</sup> These patients may also present with apneic episodes, grimacing, inconsolability, restlessness, hypertonia, stiffening, and back arching.<sup>1,2</sup> If a thorough investigation has been performed in neonates with coexisting neurological impairments with these complex comorbidities, and no identifiable source has been found, then visceral hyperalgesia should be considered, diagnosed, and properly treated.

Gabapentin has been successfully used as a treatment for visceral hyperalgesia in neonates with gastrointestinal and neurological comorbidities.<sup>2-6</sup> This is the 17th case to describe a neonate, preterm (n = 11) or term (n = 5), with neuropathic pain treated with gabapentin. In Table 2, the authors briefly describe each case by outlining the gestational age of the neonate, the pertinent neurological and gastrointestinal symptoms, the indications for starting gabapentin, initial and maintenance doses, reported side effect profile, and observed outcomes. Although there is a growing literature on the clinical responses and adverse events related to gabapentin use in neonates, both term and preterm,<sup>2-6</sup> there are no guidelines or recommendations on when or how to consider gabapentin use in neonates, to initiate and titrate the medication to effect, and to discontinue the medication.

## Pharmacokinetics of Gabapentin

Haig et al<sup>8</sup> and Ouellet<sup>9</sup> found that gabapentin exposure, the apparent total clearance of the drug from plasma after oral administration, in children less than 5 years of age is 30% less than that observed in older children when dosed on a mg/kg basis. Younger children also have a reduced plasma concentration with a starting dose of 10 mg/kg/d.<sup>8-10</sup> The medication is eliminated via glomerular filtration as unchanged drug, making

**Table 2.** Available Literature That Describes the Use of Gabapentin in Neonates.

Study	GA (weeks) and BW (g)	Pertinent Diagnosis	CNS Morbidities	GI Morbidities	Indications for Starting Gabapentin	Prior Medications	Initial Dose	Discharge Dose	Side Effects	Outcome
Behm and Kearns, 2001 <sup>6</sup>	36 <sup>57</sup> and 2475	Amyoplasia congenita Arthrogyposis Dislocated hips Clubfeet Dysplastic shoulders	NAS Pain and irritability with any movement	Nasogastric feeding tube	Pain with movements	Acetaminophen Ibuprofen	7 mg/kg once daily	10 mg/kg once daily	None	All bottle feedings Decreased pain with changing diaper Calm, not sedated, accepted pacifier
Hauer and Mackey, 2013 <sup>2</sup>	31 and NR	Prematurity Twin-twin transfusion Obstructive apnea	Cystic encephalomalacia and cerebral loss Mild spasticity	GER	Pain that was a trigger for: • Abnormal breathing patterns • Episodic hypertonia Poor sleeping patterns	Proton pump inhibitor (unspecified)	20 mg/kg/d divided TID (initiated as outpatient at 2 months of life)	Titrated to effect	NR	Improvement of irritability and sleep Resolution of apnea
Hauer and Mackey, 2013 <sup>2</sup>	25 and NR	Extreme prematurity Chronic lung disease Apnea and bradycardia Tracheostomy	Periventricular leukomalacia Episodic irritability	Gastrostomy tube Poor oral feedings	Pain that was a trigger for: • Abnormal breathing patterns • Episodic hypertonia Pain and irritability	Metoclopramide Proton pump inhibitor (unspecified)	Initial dose not stated (initiated at 5 months of life)	22 mg/kg/d divided TID	None	Decreased cardiorespiratory events Decreased irritability
Haney et al, 2009 <sup>4</sup>	39 and NR	Microduplication of chromosome 22q11.2 Pulmonary hypertension LGA	Decreased alertness Hypotonia and weak grasp	NEC Functional short gut Neonatal giant cell hepatitis Gastrostomy-jejunosomy tube Feeding intolerance Gastrostomy tube	Pain and irritability	Lorazepam Morphine Phenobarbital	5 mg/kg at bedtime	5 mg/kg morning 10 mg/kg lunch 10 mg/kg bedtime 5 mg/kg/d	Nystagmus	Improvement in the infant's tone and disposition
Edwards et al, 2015 <sup>3</sup>	23 and 670	Extreme prematurity Chronic lung disease Tracheostomy	Intraventricular hemorrhage Ventriculoperitoneal shunt Seizures Intraventricular hemorrhage Ventriculoperitoneal shunt	Gastrostomy-jejunosomy tube Feeding intolerance Gastrostomy tube	Feeding intolerance/seizures	Levetiracetam	1.5 mg/kg/d divided TID	30 mg/kg/d divided TID	Tachycardia, emesis, and agitation with abrupt discontinuation	Improved feeding tolerance
Edwards et al, 2015 <sup>3</sup>	24 and 430	Extreme prematurity Chronic lung disease	Intraventricular hemorrhage Ventriculoperitoneal shunt Seizures Hypertonia	Gastrostomy tube GER	Visceral hyperalgesia/agitation	Clonidine Diazepam Acetaminophen	20 mg/kg/d divided q12	Died	Improved feeding tolerance	Improved feeding tolerance
Edwards et al, 2015 <sup>3</sup>	24 and 860	Extreme prematurity Chronic lung disease	Seizures Hypertonia	Gastrostomy tube GER	Visceral hyperalgesia/seizures	Phenobarbital Diazepam Methadone Morphine Lorazepam Baclofen	10 mg/kg/d divided q12	Died	Decreased irritability and reduced use of benzodiazepines and morphine	Decreased irritability Improved oral feeding Toleration of gastrostomy feeds
Edwards et al, 2015 <sup>3</sup>	24 and 790	Extreme prematurity Chronic lung disease	Hypertonia	Gastrostomy tube GER	Visceral hyperalgesia/agitation	Lorazepam Baclofen	10 mg/kg/d divided q12	10 mg/kg/d divided q12	Tachycardia, emesis, and agitation with abrupt discontinuation	Decreased irritability Improved oral feeding Toleration of gastrostomy feeds

(continued)

Table 2. (continued)

Study	GA (weeks) and BW (g)	Pertinent Diagnosis	CNS Morbidities	GI Morbidities	Indications for Starting Gabapentin	Prior Medications	Initial Dose	Discharge Dose	Side Effects	Outcome
Edwards et al. 2015 <sup>3</sup>	26 and 890	Extreme prematurity Chronic lung disease	Hypertonia	Gastrostomy tube Bowel obstruction	Visceral hyperalgesia/ agitation	Baclofen Lorazepam	10 mg/kg/d divided q12	5 mg/kg/d divided q12	Bradycardia: resolved with lower dose	Weaned off benzodiazepines
Edwards et al. 2015 <sup>3</sup>	26 and 890	Twin gestation Extreme prematurity Chronic lung disease	Hypertonia	Gastrostomy tube	Visceral hyperalgesia/ agitation	Baclofen Lorazepam	10 mg/kg/d divided q12	Not applicable	Bradycardia: discontinued without trial of lower dose	
Edwards et al. 2015 <sup>3</sup>	27 and 1003	Twin gestation Congenital intestinal atresia Tracheostomy	Microcephaly Lissencephaly Seizures	Gastrostomy- jejunostomy tube	Visceral hyperalgesia/ agitation	Diazepam Phenobarbital Topiramate Baclofen	5 mg/kg q24	15 mg/kg/d divided q12		Decreased sympathetic hyperactivity Weaned off benzodiazepines
Edwards et al. 2015 <sup>3</sup>	32 and 1900	Preterm Pulmonary hypoplasia Tracheostomy	Joint contractures HIE Hypertonia	Gastrostomy tube GER	Visceral hyperalgesia/ agitation	Baclofen Lorazepam	15 mg/kg/d divided q8	15 mg/kg/d divided q12		Decreased irritability Improved oral feeding
Edwards et al. 2015 <sup>3</sup>	38 and 3500	Full term	Seizures	Gastrostomy- jejunostomy tube	Visceral hyperalgesia/ agitation/seizures	Clonidine Lorazepam Methadone Phenobarbital	10 mg/kg/daily divided q12	Not applicable		Decreased irritability Decreased use of benzodiazepines
Edwards et al. 2015 <sup>3</sup>	39 and 2940	Full term Congenital diaphragmatic hernia ECMO	NAS Seizures	Gastrostomy tube	Agitation/seizures	Clonidine Diazepam Levetiracetam Oxcarbazepine Phenobarbital Dexmedetomidine	15 mg/kg/d divided TID	15 mg/kg/d divided TID		Decreased irritability
Edwards et al. 2015 <sup>3</sup>	41 and 2921	VATER syndrome Chromosomal abnormality Pulmonary hypoplasia Tracheostomy	NAS Seizures	Gastrostomy tube	Agitation/seizures	Clonidine Diazepam Levetiracetam Oxcarbazepine Phenobarbital Dexmedetomidine Midazolam Morphine Clonidine	15 mg/kg/d divided TID	15 mg/kg/d divided TID		Decreased irritability
Brzenski and Greenberg. 2015 <sup>5</sup>	NR and 3500	Term	NAS	Poor weight gain Poor oral feedings	Extreme irritability and poor sleep	Morphine Clonidine	10 mg/kg/d divided TID	20 mg/kg/d divided TID	None	Decreased irritability Weaned off morphine and clonidine
This study	29 and 995	Premature	Myelomeningocele	Poor weight gain Poor oral feedings	Visceral hyperalgesia/ agitation	Acetaminophen	5 mg/kg once daily for 2 days, increased to 10 mg/kg/d divided Q12 for 2 days, and then increased to 15 mg/kg/d divided TID	15 mg/kg/d divided TID	None	Improved oral intake >20 g/d weight gain Improved tone

Abbreviations: BW, birth weight; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; GA, gestational age; GER, gastroesophageal reflux; GI, gastrointestinal; HIE, hypoxic ischemic encephalopathy; LGA, large for gestational age; NAS, neonatal abstinence syndrome; NEC, necrotizing enterocolitis; NR, not reported; Q, every; TID, 3 times a day; VATER syndrome, vertebral anomalies, anal atresia, tracheoesophageal fistula and/or esophageal atresia, renal and radial anomalies.

creatinine clearance the major determinant of oral gabapentin clearance and dosage adjustment necessary in patients with renal impairment.<sup>10</sup> The suggested dose of gabapentin in a safety and efficacy trial in younger children was less than 40 mg/kg/d in 3 divided doses.<sup>8</sup> Gabapentin does not bind significantly to plasma proteins and is not appreciably metabolized. Peak plasma gabapentin concentrations occur 2 to 3 hours after administration of the dose and the elimination half-life averages between 4 and 5 hours. Volume of distribution is linearly related to body weight.<sup>8,9</sup>

The 17 case reports in Table 2 have different initial starting doses and dose intervals that range from 5 mg/kg administered once daily to 20 mg/kg/d divided every 8 hours. In the study by Edwards et al,<sup>3</sup> 6 of 8 preterm infants were started on a regimen of 10 mg/kg/d divided every 12 hours. Three infants experienced bradycardia within the first 24 hours, which resolved with lower doses in 2 of the 3. None of the cases identified gastrointestinal intolerance or oversedation, and 1 case documented nystagmus after 1 month of use, which persisted throughout the remainder of treatment and resolved after discontinuation.<sup>4</sup> Nystagmus was also identified in 1 child in a case series of 9 children aged 3 months to 22 years.<sup>1</sup> In all the case series and reports, the dose and dosing intervals were titrated to effect based on clinical response and tolerability.<sup>1-6</sup> Once the symptoms were stabilized and no side effects were observed from the medication, the dose was maintained and followed accordingly. Each case report titrated to a dose below the threshold of 40 mg/kg/d divided 3 times a day (Table 2).<sup>8</sup> In our case study, the initial dose and dosing interval were titrated more conservatively than the published literature allowing for proper monitoring of the side effect profile during the titration window (Table 2).

### *Adverse Experiences of Gabapentin Use*

The side effects associated with gabapentin use in adults and children are described in Table 1 and can occur during the initiation, maintenance, or discontinuation phase. There is no clear dose escalation to side effect relationship with gabapentin as most adverse experiences occur at lower doses.<sup>10</sup> Upon initiation, side effects may include gastrointestinal intolerance, oversedation, and bradycardia.<sup>3,10</sup> The sustained use of gabapentin may lead to nystagmus that appears to resolve upon discontinuation.<sup>1,4</sup> The most common adverse experiences in adult studies are somnolence, fatigue, ataxia, and dizziness.<sup>10</sup> Recently, Edwards et al<sup>3</sup> reported a triad of tachycardia, emesis, and agitation with abrupt cessation of the medication in 2 infants who were made nil per os (NPO) for clinical deterioration (Table 2). Similar autonomic withdrawal symptoms, such as hyperactivity, irritability, and agitation, have been noted in adults who abruptly discontinue the medication.<sup>10,11</sup>

### *Dose and Interval Recommendations: Initiation and Titration*

Gabapentin can be chosen as a treatment option for visceral hyperalgesia because of its favorable side effect profile,

minimal respiratory depressive effects, and its relative lack of interaction with other medications.<sup>3,7</sup> The goal is to optimize the dose and interval to relief of symptoms while minimizing adverse effects. Based on previous case reports, the authors recommend a starting dose of 5 to 10 mg/kg administered once daily at bedtime.<sup>1,7</sup> To effectively titrate, the authors suggest increasing the dose and frequency every 1 to 2 days to a maximum of 40 mg/kg/d divided 3 times daily. If no side effects are reported from initiation of the medication and the visceral hyperalgesia symptoms are not yet stabilized, then the dosage can be titrated up accordingly. Although the upper limit appears to be 40 mg/kg/d,<sup>8</sup> only 1 case report documented a dose greater than 30 mg/kg/d.<sup>3</sup> Schwantes and O'Brien<sup>7</sup> provide a similar advancement protocol in children with a recommended starting dose of 15 mg/kg/d divided 3 times daily up to 45 mg/kg/d. Increases to 60 mg/kg/d may be needed in children, but doses greater than 60 mg/kg/d are not likely to be more effective.<sup>7</sup> Previous studies suggest that the initial dose be started at night, followed by the addition of a morning dose, and eventually an afternoon dose in carefully spaced intervals (Table 2).<sup>1,7</sup> The long-term clinical and pharmacological significance of gabapentin use for symptom relief for chronic irritability in neurologically impaired children is currently being explored in a prospective, randomized, double-blind, placebo-controlled, crossover clinical trial.<sup>12</sup>

## **Conclusion**

The diagnosis of visceral hyperalgesia should be strongly considered in neonates with neurological impairment and other coexisting gastrointestinal morbidities that are associated with a neuropathic pain response. These infants with refractory visceral hyperalgesia may benefit from gabapentin administration that should be titrated to effect and monitored closely for side effects. With increased clinical experience and research, gabapentin may prove to offer a well-tolerated and effective therapy for chronic symptoms in infants with visceral hyperalgesia.

## **Authors' Note**

This work was performed at the Goryeb Children's Hospital/Morristown Medical Center. All authors have participated in the work and take public responsibility for appropriate portions of the content.

## **Author Contribution**

JA, PL, and CR identified the case and provided clinical care to the patient. PL developed the project. JA and PA drafted the manuscript, which was then critically reviewed and approved by all authors. PL evaluated and diagnosed the patient. All authors worked in evaluation, diagnosis, and follow-up of the patient.

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## Ethical Approval

Informed consent was gained from the parents for publication of the case report.

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