Scientific Research Publishing

Open Journal of Anesthesiology, 2023, 13, 212-220
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Perioperative Care of the Adult Patient with Johanson-Blizzard Syndrome

John Nivar[1], Dennerd Ovando Jr.[1], Joe Tran[2], Lawrence Chinn[1]

[1]Rutgers New Jersey Anesthesiology Residency Program, Newark, NJ, USA
[2]Pediatric Anesthesiology at Loma Linda University Medical Center, Loma Linda, CA, USA
Email: jn475@njms.rutgers.edu

How to cite this paper: Nivar, J., Ovando Jr., D., Tran, J. and Chinn, L. (2023) Perioperative Care of the Adult Patient with Johanson-Blizzard Syndrome. *Open Journal of Anesthesiology*, **13**, 212-220.
https://doi.org/10.4236/ojanes.2023.1310019

Received: August 3, 2023
Accepted: October 28, 2023
Published: October 31, 2023

Abstract

Johanson-Blizzard syndrome (JBS) is a rare genetic disorder characterized by multiple craniofacial abnormalities, intellectual disability, sensorineural hearing loss, pancreatic exocrine insufficiency, and involvement of other organ systems to varying degrees. Patients with JBS may require surgical intervention to address the underlying phenotypic abnormalities. The many craniofacial abnormalities found in patients with JBS are a concern for the anesthesiologist. We present the case of an adult patient with JBS who is undergoing implantation of a leadless pacemaker. Considering the many cardiac and craniofacial abnormalities in these patients, the anesthesiologist should order diagnostic tests such as echocardiography to assess cardiac function, as well as be prepared to perform advanced airway techniques for difficult airways. The anesthetic provider should be aware of the varied phenotypic expression of JBS and should individualize the anesthetic plan to each patient. Prior medical literature on the anesthetic management of these patients is scarce and limited to pediatric patients. This is the first case report addressing anesthetic concerns in an adult patient with JBS.

Keywords

Johanson-Blizzard Syndrome, Anesthesia, Difficult Intubation, Pancreatic Exocrine Insufficiency, Craniofacial Abnormalities

1. Introduction

Johanson-Blizzard syndrome (JBS) was first described by pediatricians Johanson and Blizzard in 1971 [1]. JBS is a rare, autosomal recessive disorder characterized by pancreatic exocrine insufficiency, intellectual disability, sensorineural hearing loss, imperforate anus, and a multitude of craniofacial abnormalities, including a short nose, absent alae nasi, a receding chin, maxillary hypoplasia, mi-

crognathia, microcephaly, a high arched palate, and absent permanent teeth [2] [3] [4] [5]. Since its first description in literature, JBS case reports only exist in pediatric patients. This is the first published case report on an adult patient with JBS. Previous case reports have focused almost entirely on the pediatric population. A previous case report on a 3-year-old patient mentions that JBS makes routine airway management difficult and that the involvement of multiple organ systems further complicates these cases [2]. We present the case of a 66-year-old female with a medical history significant for JBS, hypertension, non-insulin dependent diabetes mellitus, congestive heart failure, aortic stenosis s/p aortic valve replacement, who underwent general anesthesia to receive a leadless pacemaker implantation for sick sinus syndrome. The patient, non-verbal at baseline, required preoperative sedation secondary to agitation and lack of cooperation with the medical staff. The anesthetic course was uncomplicated, and the patient was intubated on the first attempt. Intraoperative glucose monitoring was not performed given the short nature of the case.

2. Case Report

A 66-year-old obese female presented to Newark University Hospital for elective implantation of a leadless pacemaker for sick sinus syndrome (SSS). She had recently suffered several episodes of light-headedness and palpitations which prompted her to reach out to her primary medical provider who referred her for the pacemaker. Her past medical history was significant for Johanson-Blizzard Syndrome (JBS), hypertension that was well-controlled on Lisinopril, non-insulin dependent diabetes mellitus on metformin, congestive heart failure with preserved ejection fraction, and aortic stenosis status-post aortic valve replacement. The patient arrived at the hospital from a long term assisted care facility. She had severe intellectual disability and was non-verbal at baseline, which limited her ability to understand and interact with the medical team.

The patient's admission vital signs were within normal limits. She was breathing comfortably and in no apparent distress. She had not eaten anything for greater than eight hours and was appropriately NPO for the procedure. Given the patient's extensive cardiac history, an ECG was obtained on admission. The ECG (**Figure 1**) demonstrated normal sinus rhythm with no axis deviation, atrioventricular block or sinus arrest and a normal QTc interval. This patient with a history of heart failure with preserved ejection fraction had an echocardiogram obtained one month prior to her admission, which demonstrated an ejection fraction of 66% with no wall motion abnormalities. On arrival at the cardiac catheterization lab, the patient immediately became anxious and agitated. A one-time order of lorazepam 2 mg intravenous was ordered and administered. The patient's agitation subsequently improved, and she was able to be positioned supine on the operating room table. Standard ASA monitors including pulse oximeter, ECG leads for heart monitoring, blood pressure cuff, temperature probe, and oxygen with end-tidal CO_2 were then applied. The airway exam was difficult to conduct secondary to lack of cooperation from the patient. On visual

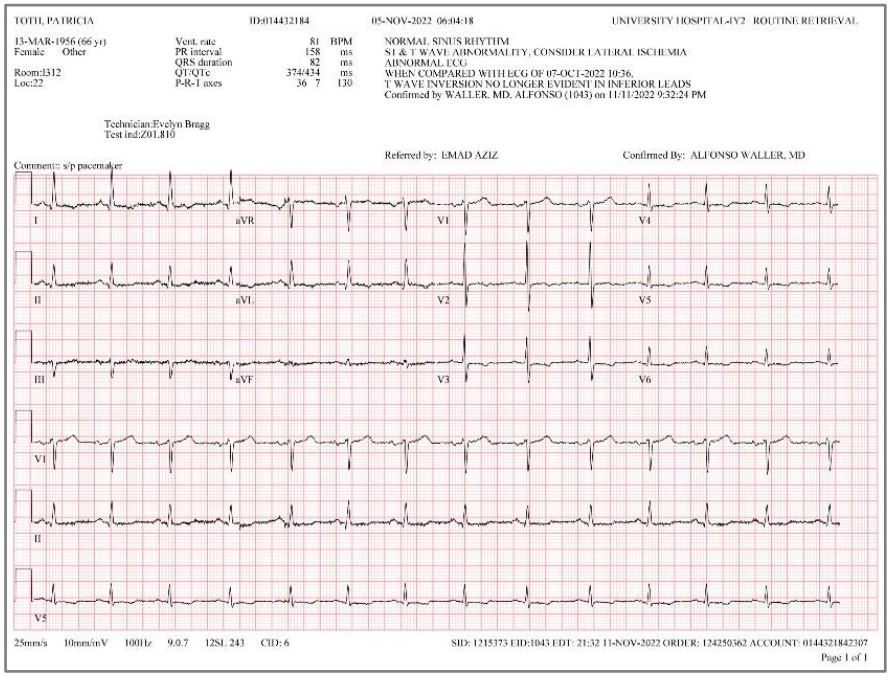

Figure 1. ECG demonstrating normal sinus rhythm with no acute pathology.

inspection, a large tongue and thick neck were appreciated, as well as poor dentition with multiple missing teeth and we were unable to visualize the uvula and most of the oropharynx. The patient's thyromental span measured at greater than 3 fingerbreadths and she had a full range of motion of the neck. There were no signs of fluid overload or decompensation from her history of heart failure at this time.

For induction, the patient received intravenous 12 mg etomidate, 40 mg rocuronium, and 30 mg propofol that was mixed with 80 mg lidocaine in the same syringe. Intubation was initially attempted via direct laryngoscopy with a 3.0 Macintosh blade and a 7.0 mm endotracheal tube (ETT). The vocal cords were visualized, however the ETT was not able to be passed through the vocal cords and we were not able to proceed with direct laryngoscopy. A second attempt with video laryngoscopy (C-MAC) and a 6.5 ETT with a rigid intubating stylet was successful. During the second attempt, the ETT was gently "corkscrewed" through the vocal cords. The patient was noted to have a narrow glottic opening. Endotracheal tube placement was confirmed by chest auscultation and capnometry. Intraoperatively, the patient received a total of 1 liter of Ringer's lactate and remained hemodynamically stable throughout the entirety of the procedure. She did not require blood transfusions or any other blood products during the surgery. The procedure lasted approximately one hour and the patient was extubated afterwards without having any complications. She was then transferred to the post anesthesia care unit (PACU) where her vital signs would remain stable prior to being transferred to the cardiac care unit (CCU). She was fully awake at this time and able to protect her airway with no gagging or coughing from secretions. She was then transferred to the CCU where she would remain on tele-

metry monitoring overnight. She had an uneventful stay in the CCU and was subsequently discharged the following day by the primary medical team to her long-term health care facility. Her primary caregiver was instructed to have the patient follow up with her cardiologist in two weeks for continued surveillance of her SSS.

The patient had a follow up appointment with her cardiologist approximately two weeks after the surgery for implantation of leadless pacemaker. At her appointment she had no complaints related to her device and no arrhythmias. She had no complaints of palpitations or dizziness. The surgical site was clean and intact with no signs of infection. The device was interrogated by her cardiologist and this revealed no arrhythmias since implantation. Device longevity was estimated to be approximately 22 years. The patient was instructed to follow up with her cardiologist again in 6 months and sooner if she has any complications.

3. Discussion

Johanson-Blizzard Syndrome (JBS) is an extremely rare genetic condition caused by mutations in the UBR1 gene, which codes for an E3 ubiquitin ligase involved in protein degradation [6]. The frequency of JBS has been estimated to be about 1 in 250,000 births [7]. Since its first description by Johanson and Blizzard in 1971, JBS has been reported in medical literature in more than 60 cases. Males and females are believed to be equally affected by JBS [8]. Despite this condition having hallmark features such as hypoplastic nasal alae, hearing loss, and pancreatic exocrine insufficiency, the phenotypic presentation of JBS is widely variable. Due to its wide genetic variability, no two JBS patients share the exact same phenotypic features. Prior anesthetic literature dealing with the perioperative care of JBS patients is scarce, limited only to a handful of pediatric case reports. Here, we describe the case of an adult patient with JBS and describe the most pertinent disease characteristics the anesthesiologist should be aware of when providing care for these patients.

There are several factors that the anesthesiologist must consider in the perioperative management of the patient with JBS. Among these, facial dysmorphisms are the most salient features found in JBS and are of special concern. Micrognathia of both the maxilla and mandible have been reported in JBS [9], as well as a high arched palate. Dental abnormalities are common in JBS and include oligodontia, malformed deciduous and permanent teeth, complete absence of permanent teeth, and enamel hypoplasia [4] [7] [10]. JBS classically involves abnormal formation or even absence of the structural cartilage and supportive connective tissue of the nose with a decreased length from nasal root to the nasal tip and a thin or deficient nasal ala leading to nasal alar hypoplasia and a characteristic "beaked nose" appearance. Although not an exhaustive list, these facial malformations can complicate airway management and lead to difficulty with bag mask ventilation as well as endotracheal intubation. In our instance, our intubation attempt was complicated by a narrow glottic opening which required intubation with a small diameter endotracheal tube in order to avoid

causing damage to the vocal cords. Given that difficult airways should be anticipated in a patient with JBS, a prior case report on the anesthetic care of JBS patients recommended an inhalational induction with maintenance of spontaneous ventilation. Tracheal intubation can then be performed while the patient is under deep sevoflurane anesthesia. Regardless of the method of induction, the anesthesia provider should be aware of the challenges in airway management seen in JBS patients and tailor the anesthetic plan accordingly. A difficult airway cart is necessary and should be ready and available when the anesthesiologist is managing a JBS patient's airway.

The range of intellectual disability (ID) seen in JBS varies from mild to severe. The administration of anesthesia to patients with ID, regardless of the underlying etiology, can be particularly challenging. Lack of patient cooperation and an inability to communicate are common obstacles the anesthetic provider may face when providing care for this unique patient population. The patient's inability to comprehend the medical procedure and the unfamiliarity of the hospital setting may precipitate agitation and aggression. Additionally, JBS patients frequently present with bilateral sensorineural hearing impairment which can further create communication blocks and contribute to their agitation, causing the patient to be uncooperative. In our case, our patient became agitated and was uncooperative with the medical staff while attempting to transfer her from the stretcher to the OR bed. We administered 2 mg of midazolam intravenously with subsequent improvement in her agitation. A case series from China involving 29 JBS patients reported a 59% incidence of sensorineural hearing loss. This is believed to be secondary to cystic malformations of the cochlea and vestibular system. Any underlying deafness can further impede communication with JBS patients and further contribute to a patient's agitation.

Varying degrees of hypotonia characterizes multiple genetic syndromes, and JBS is not an exception, with multiple instances noted in previous case reports. Patients with hypotonia have underlying degrees of respiratory muscle weakness and, depending on the severity, may have poor preoperative pulmonary function. If undergoing general anesthesia, these patients may require postoperative ventilation and the need for careful respiratory monitoring in an intensive care unit. Patients with pre-existing hypotonia may also have an increased sensitivity to non-depolarizing neuromuscular blockers.

A sine qua non of JBS is pancreatic exocrine insufficiency, which affects 80% - 99% of these patients [1] [11]. This can lead to fat malabsorption and electrolyte imbalances. A comprehensive metabolic panel should be drawn, and electrolytes should be optimized prior to surgery. Both diarrhea and constipation are common, and the patient can be predisposed to aspiration of undigested stomach contents if not properly fasting. The malabsorption associated with pancreatic exocrine insufficiency leads to impaired absorption of fat-soluble vitamins such as vitamin K. Deficiency of vitamin K is especially concerning as it could affect coagulation and increase bleeding risk during surgery. This may warrant assessing coagulation markers prior to a patient's procedure. Decreased absorption of

Vitamin D can lead to signs and symptoms of hypocalcemia, such as muscle tetany and seizures. An additional characteristic feature of JBS is the varied axial skeletal abnormalities. These abnormalities may lead to delayed skeletal maturation which will ultimately result in the patient having a short stature. The skeletal abnormalities may be exacerbated by the malabsorption that results from pancreatic exocrine insufficiency and leads to deficiency of some of the fat-soluble vitamins such as vitamins A, D, and E, to name a few. Sacral hiatus abnormalities may also be seen in some patients with JBS, and this is an important consideration for the anesthesiologist if attempting to perform epidural or spinal injections. Hypocalcemia can be detrimental to a patient's underlying myocardial contractility and vascular tone and should be corrected whenever possible.

Endocrine dysfunction can also be seen in JBS patients [5] [7] [12]. Endocrine pancreatic insufficiency is not as common as exocrine dysfunction, but it has been described in prior case reports. Both insulin-dependent and insulin-independent diabetes mellitus have been previously described in JBS patients. Patients with any form of endocrine pancreatic dysfunction should have close monitoring of their blood glucose level. A preoperative and postoperative glucose level should be obtained and treated accordingly. Intraoperative glucose monitoring will depend on patient (*i.e.*, HbA1c and current glycemic control, type of medications used for glucose management, etc.) and surgical factors (*i.e.*, duration of surgery, expected fluid shifts, etc.) and a plan for glucose monitoring should be tailored to each patient by the anesthesia provider. Our patient had a history of type 2 diabetes mellitus that was being managed with oral metformin. Her metformin was stopped 48 hours prior to her surgery. She was euglycemic prior to surgery. Post-operatively, her glucose levels ranged from 118 to 191. Given the short duration of her procedure (less than one hour), we did not monitor glucose levels intra-operatively. The endocrinopathies seen in JBS are not only limited to the pancreas. Hypopituitarism [11] [12] and hypothyroidism have also been reported. Hypothyroidism may be an issue during the intraoperative period, as it may lead to potential temperature dysregulation and hypothermia which can affect the patient's postoperative course. Hypopituitarism, depending on the hormones affected, can lead to diverse manifestations such as adrenergic insufficiency due to ACTH deficit or polyuria/polydipsia from ADH deficiency.

Gastrointestinal manifestations of JBS are varied and less common but include GERD and anorectal anomalies such as anteriorly placed or imperforate anus. Imperforate anus may be diagnosed and treated early on after birth. Our patient presented with a history of GERD that was being treated with a proton pump inhibitor. GERD is a well-known risk factor for pulmonary aspiration and rapid sequence induction may be indicated for patients with severe, uncontrolled GERD. Any patient with unrepaired imperforate anus may also require a rapid-sequence intubation, especially if the abdomen is distended. Due to their pancreatic insufficiency and other gastrointestinal manifestations, JBS patients have frequent episode of diarrhea which leads to intestinal malabsorption. Exocrine pancreatic insufficiency doesn't always present as an initial sign or symp-

tom, but it is believed that all patients will ultimately develop some degree of pancreatic insufficiency, which is the known as the hallmark feature of JBS. Liver disease is not classically associated with JBS, although one prior case report described a patient with severe cholestatic liver disease that progressed to liver fibrosis and portal hypertension. Liver disease can have a whole host of implications for the anesthesiologist and necessitates close monitoring.

Hematologic abnormalities are not common in JBS and, in the setting of pancreatic insufficiency, point more towards a diagnosis of Shwachman-Diamond syndrome, a similar genetic condition characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities. Severe anemia and thrombocytopenia have only been described in one prior case report of JBS. Mild leukopenia has also been described in several patients, and this is a special consideration for the anesthesiologist when caring for the perioperative patient with JBS. A 5-month-old patient with features characteristic of JBS was found to have severe anemia requiring multiple blood transfusions. The infant had two previous siblings who had suspected JBS and also required frequent blood transfusions for significant anemia prior to dying at ages 4 months and 4.5 months, respectively. Apart from anemia, the patient also presented with mild to moderate thrombocytopenia. Although difficult to make recommendations based on a single case report and a paucity of data and literature on JBS, obtaining pre-operative labs (*i.e.*, complete blood count, basic metabolic panel) on JBS patients should be considered and tailored to a patient's history and physical exam.

There are many cardiac anomalies associated with JBS. These include, but are not limited to: pulmonary atresia, transposition of the great arteries, total anomalous pulmonary venous return with a common atrium, thoracic situs inversus with or without dextrocardia, ventricular septal defects, and atrial septal defects [13] [14]. Although not a usual part of the JBS spectrum, this again attests to the wide and varied range of organ involvement seen in this syndrome. A full cardiac evaluation (*i.e.*, ECG, echocardiogram) should be considered for these patients prior to proceeding with sedation and/or anesthesia.

Genitourinary symptoms are far less common in patients with JBS but they have been reported in several cases [15]. The most common genitourinary symptoms ascribed to patients with JBS include vesicoureteral reflux and hypospadias. Hypospadias can be diagnosed immediately at birth and treated with surgery. Vesicoureteral reflux initially presents with recurrent febrile urinary tract infections (UTI) in young patients. These UTIs will respond to appropriate antibiotic therapy and then recur. Diagnosis is by voiding cystourethrogram which would show reflux of urine from the bladder back into the ureter and up to the kidneys. These patients may require prophylactic antibiotic therapy to prevent fibrosis of the renal pelvis and ureters due to repeated bouts of UTIs. Our patient did not present with any GU manifestations.

4. Summary

In summary, we present the case of an adult patient with Johanson-Blizzard Syn-

drome (JBS), who presented to the emergency department for an elective implantable leadless pacemaker in the setting of sick sinus syndrome. Due to the extreme rareness of JBS, there is scarce literature available on this condition. This report represents the first described case of an adult with JBS undergoing anesthesia. There is a paucity of existing literature regarding JBS, and the current cases describe only the anesthetic management of pediatric patients with this condition. Patients with cardiovascular anomalies require echocardiogram prior to administration of anesthetics, as these cardiovascular conditions can complicate the intraoperative course. Considering the varied phenotypic manifestations and numerous dysmorphic features that these patients present with, the anesthesiologist should be equipped and trained to perform advanced airway management techniques. Video laryngoscopy and other assistive devices such as cricoid pressure and intubating stylets should be readily available in the management of the JBS patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Johanson, A. and Blizzard, R. (1971) A Syndrome of Congenital Aplasia of the Alae nasi, Deafness, Hypothyroidism, Dwarfism, Absent Permanent Teeth and Malabsorption. *J Pediatr*, **79**, 982-987. https://doi.org/10.1016/S0022-3476(71)80194-4

[2] Fichter, C.R., Johnson, G.A., Braddock, S.R. and Tobias, J.D. (2003) Perioperative Care of the Child with the Johanson-Blizzard Syndrome. *Pediatric Anesthesia*, **13**, 72-75. https://doi.org/10.1046/j.1460-9592.2003.00957.x

[3] Alpay, F., Gul, D., Lenk, M.K., *et al.* (2000) Severe Intrauterine Growth Retardation, Aged Facial Appearance, and Congenital Heart Disease in a Newborn with Johanson-Blizzard Syndrome. *Pediatric Cardiology*, **21**, 389-390. https://doi.org/10.1007/s002460010089

[4] Gould, N.S., Paton, J.B. and Bennet, A.R. (1989) Johanson-Blizzard Syndrome: Clinical and Pathological Findings in 2 sibs. *American Journal of Medical Genetics*, **33**, 194-199. https://doi.org/10.1002/ajmg.1320330212

[5] Kristjansson, K., Hoffman, W.H., Flannery, D.B., *et al.* (1988) Johanson-Blizzard Syndrome and Hypopituitarism. *The Journal of Pediatrics*, **113**, 851-853. https://doi.org/10.1016/S0022-3476(88)80015-5

[6] Zenker, M. (2008) UBR1 and the N-End-Rule Pathway and the Johanson-Blizzard Syndrome. In: Epstein, C.J., Erickson, R.P. and Wynshaw-Boris, A., Eds., *Inborn Errors of Development: The Molecular Basis of Clinical Disorders of Morphogenesis*, 2nd Edition, Oxford University Press, New York, 1190-1194.

[7] Prakash, C. and Clouse, R.E. (2003) Johanson-Blizzard Syndrome. NORD Guide to Rare Disorders. Lippincott Williams & Wilkins, Philadelphia, 208-209.

[8] Gorlin, R.J., Jr. Cohen, M.M. and Hennekam, R.C.M. (2001) Syndromes of the Head and Neck. 4th Edition, Oxford University Press, New York, 1010-1012.

[9] Corona-Rivera, J.R., Zapata-Aldana, E., Bobadilla-Morales, L., Corona-Rivera, A., Peña-Padilla, C., Solis-Hernández, E., Guzmán, C., Richmond, E., Zahl, C., Zenker,

M. and Sukalo, M. (2016) Oblique Facial Clefts in Johanson-Blizzard Syndrome. *American Journal of Medical Genetics Part A*, **170**, 1495-1501. https://doi.org/10.1002/ajmg.a.37630

[10] Rezaei, N., Sabbaghian, M., Liu, Z.F. and Zenker, M. (2011) Eponym: Johanson-Blizzard Syndrome. *European Journal of Pediatrics*, **170**, 179-183. https://doi.org/10.1007/s00431-010-1240-5

[11] Jones, N.L., Hofley, P.M. and Durie, P.R. (1994) Pathophysiology of the Pancreatic Defect in Johanson-Blizzard Syndrome: A Disorder of Acinar Development. *The Journal of Pediatrics*, **125**, 406-408. https://doi.org/10.1016/S0022-3476(05)83286-X

[12] Hoffman, W.H., Lee, J.R., Kovacs, K., Chen, H. and Yaghmai, F. (2007) Johanson-Blizzard Syndrome: Autopsy Findings with Special Emphasis on Hypopituitarism and Review of the Literature. *Pediatric and Developmental Pathology*, **10**, 55-60. https://doi.org/10.2350/06-05-0085.1

[13] Wilschanski, M. (2008) Other Hereditary and Acquired Pancreatic Disorders. In: Kleinman, R.E., Goulet, O.J., Mieli-Vergani, G., *et al.*, Eds., *Walker's Pediatric Gastrointestinal Disease*, BC Decker, Inc. Hamilton, Ontario, 1252-1254.

[14] Helin, I. and Jodal, U. (1981) A Syndrome of Congenital Hypoplasia of Alae Nasi, Situs Inversus and Severe Hypoproteinemia in Two Siblings. *The Journal of Pediatrics*, **99**, 932-934. https://doi.org/10.1016/S0022-3476(81)80026-1

[15] Almashraki, N., Abdulnabee, M.Z., Sukalo, M., Alrajoudi, A., Sharafadeen, I. and Zenker, M. (2011) Johanson-Blizzard Syndrome. *World Journal of Gastroenterology*, **17**, 4247-4250. https://doi.org/10.3748/wjg.v17.i37.4247