

# NEONATOLOGY TODAY

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## Variations of Coronary Origin: A Case of Bland White Garland Syndrome via 64 Slice Cardiac CT Angiography

By Shah Azmoon, MD; Matthew Budoff, MD; FACC, FAHA, FSCAI; and David Atkinson, MD

### Abstract

**Background:** Anomalies of the coronary arteries have been described as early as the 1800s. In 1933, Drs. Bland, White and Garland described the clinical syndrome of heart failure seen in infants with anomalous origin of the left coronary artery arising from the pulmonary artery. Mortality rates have been reported to be greater than 90% within the first year of life if left untreated. Two dimensional echocardiography with Doppler color flow mapping has been frequently used for initial diagnosis, whereas conventional coronary angiography remains the gold standard.

**Case Presentation:** Here we present a case of Bland White Garland Syndrome in which the left coronary arteries arise from the pulmonary artery in a symptomatic young child. Diagnosis was promptly made using 64 slice Cardiac CT Angiography after failed attempts in diagnosis using other modalities and the patient was sent for surgical correction. Using low dose protocols, the estimated radiation dose to the infant was 1 milliseivert.

**Conclusion:** The high spatial and temporal resolution of 64 slice cardiac CT angiography may provide an alternate imaging modality in the diagnosis of congenital coronary anomalies, avoiding invasive risks of conventional coronary angiography.

### Manuscript

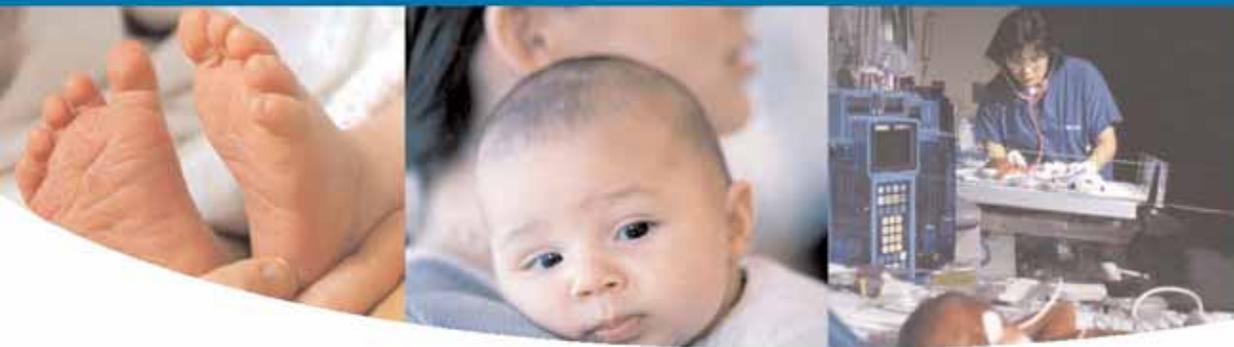
Early in fetal myocardial development the myocardium is nourished via myocardial sinusoids where persistence of the sinusoids may lead to coronary aberrancy and fistulae. Coronary vessel formation begins approximately at 32 days of gestation. In as many as 50% of the population, the right coronary artery (RCA) and its conal branch may originate separately (normally single origin from the right coronary cusp). Similarly, in approximately 1% of patients the left anterior descending artery (LAD) and the left circumflex coronary artery (LCx) may originate separately (normally from the left main artery (LM) via the left coronary cusp). Location of these cusps on the aorta may vary and while most may be inconsequential, a high origin of a coronary ostium may reduce diastolic coronary artery blood flow[1]. More importantly, origination of LAD or a single left coronary arising from the right sinus of Valsalva and even origination of the RCA from the left side can have deleterious effects, as it may course between the pulmonary arteries and aorta prior to reaching the left ventricle. Vig

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orous expansion of these large vessels, especially with exercise, can compress the coronaries leading to myocardial ischemia and even sudden cardiac death[2-4]. Despite the low incidence of anomalous coronary arteries (< 0.64% of live births[5]), such an anomalous course carries a high mortality due to sudden cardiac death (SCD) in young athletes under the age of 35 years (13%); only second to hypertrophic cardiomyopathy in this age group[6-8]. The most common anomalous origin of a coronary artery is the right-sided origination of the LCx and, when arising from the RCA, it usually has a posterior course to the left ventricle avoiding vigorous contact with larger vessels. Anomalous origin of coronaries has been associated with other congenital heart defects including Tetralogy of Fallot (9%)[9-10].

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***“The high spatial and temporal resolution of 64 slice cardiac CT angiography may provide an alternate imaging modality in the diagnosis of congenital coronary anomalies avoiding invasive risks of conventional coronary angiography.”***

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Anomalous origin of the coronaries from the pulmonary artery (PA) has been documented as far back as the 1800s.[11-12] While most coronary anomalies arise from the aorta, less than 0.4% of patients with congenital cardiac anomalies may have origination of their coronary vessels from the PA (~ 1 in 300,000 live births in the US)[13]. Abnormal division of the cono-truncus into the aorta and PA or abnormal involution and persistence of an endothelial bud on a pulmonary sinus may lead to an aberrant connection to the developing coronary artery. In 1933, Drs. Bland, White and Garland, who, at autopsy, diagnosed the syndrome of early progressive heart failure associated with anomalous origin of the coronary arteries arising from the PA in a 3-month old child, whose father would be the future chairman of radiology at Massachusetts General Hospital[14]. Most commonly, the anomaly is a single left coronary rather than the RCA and in some instances the LCx and LAD may have separate origins from the PA[15-18]. While the clinical presentation may vary depending on the coronary involved as well as its size and distribution, there exists significant hemodynamic compromise in most cases with ensuing myocardial ischemia and progressive ischemic cardiomyopathy. Untreated, mortality has been reported as high as 90% within the first year of life[18]. In the less common variant where both the left and right coronaries arise

from the PA, prompt diagnosis and treatment is necessary as such a circumstance is not compatible with survival.

Symptoms of angina in an infant may include: feeding intolerance, irritability or respiratory distress when crying, diaphoresis, pallor, failure to thrive or even shock. Early symptoms may temporarily be masked by the presence of large collateral vessels and rarely child onset symptoms may include precordial pain, dyspnea, tachypnea, shortness of breath, exertional chest pain, syncope or even sudden cardiac death. Upon normalization of the physiologically-elevated neonatal pulmonary vascular resistance in the first four to six weeks of infancy, the low perfusion pressures and low oxygen saturation characteristic of the PA lead to myocardial ischemia and progressive cardiomyopathy. Demand ischemia due to anomalous coronaries from the PA is not noted prenatally because of the parallel circulatory system providing relatively equivalent oxygen concentrations as well as equivalent pressures between the aorta and main pulmonary artery through the patent ductus arteriosus (PDA). With the formation of collateral blood supply between the right and left coronary systems, symptom onset may be delayed, however, coronary steal phenomenon may occur from the higher pressure collateral vessels and retrograde flow into the PA from the anomalous coronary should collaterals arise from normal coronaries[19-21]. A “step up” in oxygen saturation within the PA may be detected on cardiac catheterization in lieu of the left to right shunt, with the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) ranging from 1-1.5. Untreated, coronary steal will exacerbate symptoms of heart failure and accelerate complications of ischemia, cardiomyopathy and pulmonary hypertension. Although anomalous coronary origination is usually an isolated defect, association with other congenital heart defects such as patent ductus arteriosus, coarctation of the aorta, ventricular septal defect, Tetralogy of Fallot and Hypoplastic Left Heart Syndrome have been noted.[22].

Here we present a case of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). J.O. was born in the Philippines at 8 lbs 2 oz, term without complications. There existed no family history of significant disease, maternal radiation exposure or intake of teratogenic drugs. At 9 months of age, she presented with symptoms of chronic cough and shortness of breath and found to have cardiomegaly on routine chest X-ray. A two dimensional echocardiogram revealed dilated cardiomyopathy (CM) with a left ventricular (LV) ejection fraction (EF) of approximately 20% with LV thrombus. Patient’s family was informed she would need to be on lifetime digoxin and captopril and diagnosed with a history of CM presumed secondary to viral myocarditis. Within the following year J.O.’s family immigrated to the US where she would run out of medications, and was unable to seek medical care for several months.

In patients with ALCAPA chest roentogram may demonstrate cardiomegaly with or without pulmonary vascular congestion, although this is not diagnostic. Aside LV hypertrophy, abnor-



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Image 1a: A trans-thoracic echocardiogram with the patient's left main coronary appearing to originate from the pulmonary artery.

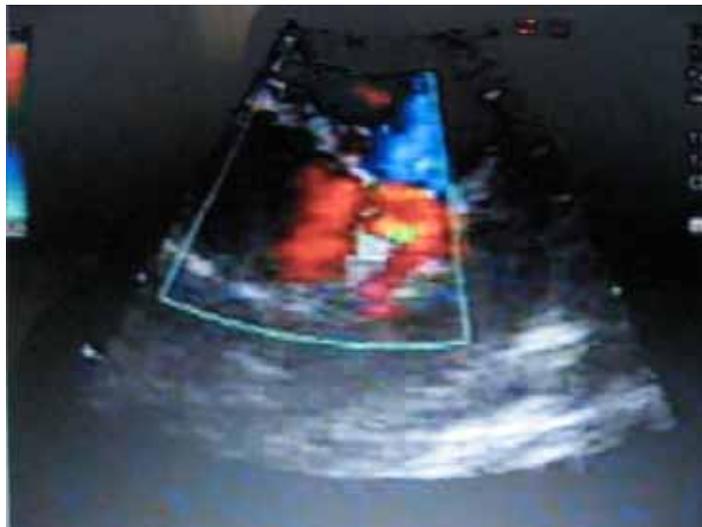


Image 1c: A trans-thoracic echocardiogram with retrograde flow (in red) through the patient's left coronary into the pulmonary artery.

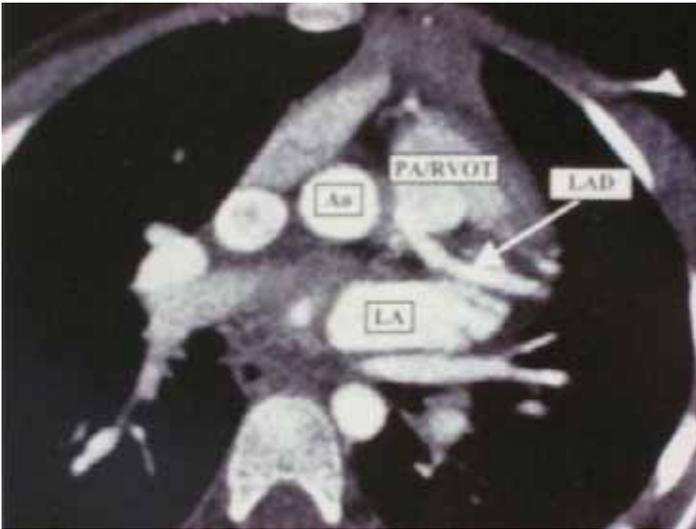


Image 1b: A trans-thoracic echocardiogram with apparent retrograde flow (in red) through the patient's left coronary.

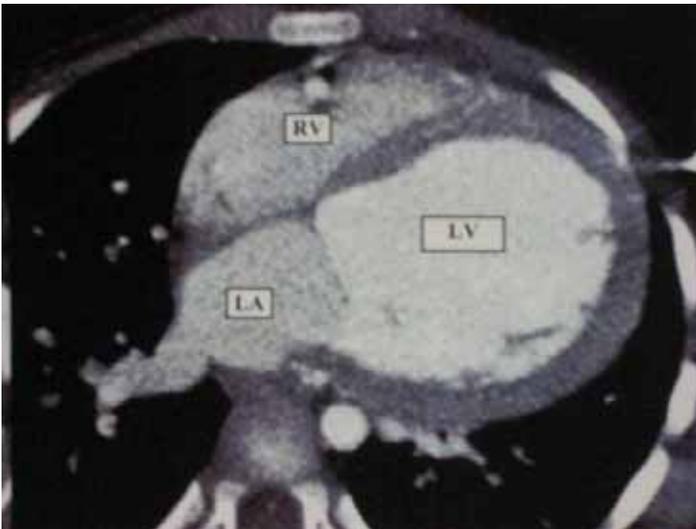
malities of repolarization detected as ST segment depression and/or inversion in the inferior and lateral leads may be noted on electrocardiogram (ECG) along with wide, deep Q waves in the lateral leads with poor R wave progression. On trans-thoracic echocardiogram (TTE) LV dysfunction, mitral regurgitation or mitral annular dilation and wall motion abnormalities in the setting of left heart dilatation may be seen. Enlargement of the proximal right coronary artery may reflect development of extensive collateralization. While most cases of ALCAPA may be diagnosed with echocardiography, two dimensional echo alone may be inadequate as the close course of the anomalous coronary to the aortic sinus may create a false impression of normal anatomic origin (Images 1a-1c). Use of color-flow Doppler imaging has largely avoided the need for cardiac catheterization by providing significantly increased diagnostic accuracy with demonstration of abnormal retrograde anomalous coronary flow, although dependent on PA pressures and development of collaterals. However, echocardiographic diagnosis even with Doppler

may be difficult should the anomalous coronary arise from a branch pulmonary artery. While retrograde flow into the PA is usually directed in an unusual orientation, improper diagnosis of a PDA shunt or coronary-cameral fistula can be erroneously made. Lack of collateralization may also make identification of ALCAPA by selective right coronary arteriography or aortography difficult in the cath lab, while stop flow angiography may result in a high rate of false-negatives due to incomplete occlusion of the PA. Use of trans-esophageal echocardiography is seldom necessary in infants.

J.O. presented to our clinic with parental complaints of intermittent episodes of nighttime diaphoretic spells and a history of viral CM. On physical examination she was found to be in no apparent distress, acyanotic and 50th percentile for height and weight. Her blood pressure was 93-126/44-77 mmHg; she had a heart rate of 75-125 beats per minute, was afebrile, had a respiratory rate of 20-24, and an oxygen saturation level of 98% on room air. Cardiac examination revealed a visible and lateralized point of maximal intensity, normal rate and rhythm, a 4th heart sound and II/VI holosystolic blowing murmur of mitral regurgitation. A soft continuous murmur may resemble a persistent PDA with flow from the aorta to the pulmonary circulation or via collateral vessels. Breath sounds were clear bilaterally, without hepatomegaly on abdominal exam and symmetric normal amplitude pulses in all extremities. Her chest radiograph was significant for cardiomegaly without evidence of acute venous congestion. Electrocardiogram revealed sinus tachycardia, Q waves in Lead I and aVL and inferior ST segment depression with T wave inversion suggestive of ischemia in the inferolateral distribution with abnormalities of repolarization. An initial TTE evaluation revealed an EF 15% with appearance of LV thrombus and spontaneous contrast, massively dilated CM with turbulent flow and a small pericardial effusion. The patient was admitted for anticoagulation and further workup of CM which also included a negative Gallium scan as well as mildly elevated PA pressures on right heart catheterization. Repeat TTE during the course of the admission showed resolution of thrombus, EF ~ 25% with appearance of left coronary in some views to arise from the aortic root with a coronary to main PA



*Image 2a: A cardiac CT angiography depicting patient's left main coronary anomalously originating from the pulmonary artery / right ventricular outflow tract.*



*Image 2b: A cardiac CT angiography revealing our 2 year old patient's marked left ventricular dilatation*

fistula while in other views it appeared the left coronary would originate directly from the PA. The patient was referred for cardiac CT angiography (CCTA) for better delineation of coronary anatomy (Images 2a-2b).

More than 35 years after diagnosis by Drs. Bland, White and Garland of what is now known as ALCAPA, Drs. Sabiston, Neil and Taussig first showed retrograde flow via an anomalous coronary into the PA with effective treatment by ligation of the anomalous coronary at the junction of the PA. Today, generally surgical intervention is recommended for treatment of anomalous coronary artery when increased risk of ischemia or serious ventricular arrhythmias exists with surgical mortality rates quoted at less than 5-10% by most congenital heart surgery programs[23]. In the case of anomalous coronaries arising from the PA, surgical correction is necessary to avoid further strain on the heart and progressive cardiomyopathy. Surgical procedure of choice remains the direct anastomosis of the anomalous coronary from the PA to the aorta, first described in 1970s. In those young patients in which the anomalous coronary position is not suitable for direct transfer creating an intrapulmonary aorto-coronary tunnel may be required, as described by Takeuchi and colleagues in 1979. However, this procedure may result in tunnel stenosis, aortic regurgitation or pulmonary artery stenosis[23]. When significant cardiac dysfunction is present evaluation for cardiac transplantation may be necessary. While coronary anomalies may also be corrected by coronary artery bypass grafting or stenting, percutaneous treatment options for coronary anomalies of pulmonary origin do not exist[24-25]. Prognosis after surgical correction is frequently excellent with improvement of global left ventricular dysfunction or mitral regurgitation, however patients are still susceptible to atheromatous as well as non-atheromatous coronary stenoses. Acute coronary takeoff with non-atheromatous ridge formation, coronary hypoplasia, myocardial bridging or surgical reimplantation of coronaries may lead to increased risk of coronary stenosis[26-28]. Coronary enlargement, which tends to increase with age, may also occur when collateral vessels are of normal origin and coronary steal is present[29].

While, traditionally cardiac catheterization has been used as the gold standard for diagnosis of coronary anomalies, angular restriction of angiographic projections and limitations by its planar imaging nature may render conventional angiography less useful for a more clear anatomic picture when compared to newer imaging modalities. Conventional angiography is also invasive and carries a morbidity and mortality rate of 1.5% and 0.15%, respectively[30]. With progressive improvement in both resolution and technical specifications, as well as multi-planar reconstruction with maximum intensity projections and volume rendering, cardiac CT angiography may be an adequate alternative diagnostic tool in the detection of coronary anomalies. While in younger patients a short investigation time and minimal after care provides practical usefulness, multi-angle assessment using three dimensional reconstruction can provide optimal vessel projection for evaluation of surgical intervention and thus avoid the repeated exposure to radiation and contrast required with conventional angiography. Clinical usefulness of CCTA in evaluation of infants with complex congenital heart



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diseases has been successfully evaluated[31], and published reports have also noted superiority of CCTA in defining ostial origins and proximal paths of anomalous coronaries when compared to conventional angiography[32]. More importantly, we hope to draw attention with this case of ALCAPA to the need for early recognition of coronary anomalies when presented with clinical symptoms of heart failure or ischemia in infants.

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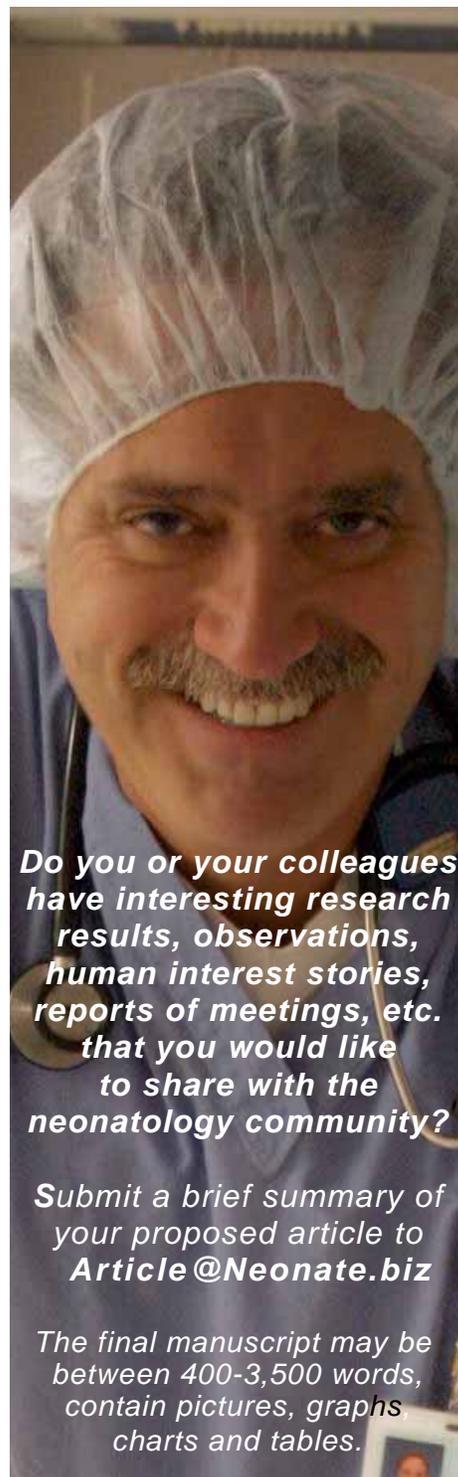
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By Amed Soliz, MD

## Introduction

*Babies Without Borders* (BWB) is a non-profit organization of people concerned with the high rates of infant and neonatal mortality and morbidity in the developing world, who are willing to put forth their own voluntary efforts to effect change. There are many organizations that provide much needed assistance and services to developing countries. However, it is very clear that the need for such assistance is endless. The mission of *Babies Without Borders* is to offer on-site education to host facilities in developing nations, and to afford those personnel the basic tools and materials they need to provide a higher level of ongoing medical care through a network of voluntary medical personnel. The vision of *Babies Without Borders* is to dramatically lower rates of morbidity and mortality from easily preventable causes in infants in developing countries. The primary objective of *Babies Without Borders* is to help ameliorate suffering, and to promote better health care practices through practical and humanitarian interventions, including hands-on care, education, and outreach programs. *Babies Without Borders* has developed seven primary programs to improve the survival and outcomes of these most vulnerable babies ("Practical Education, Bags of Life, Bubbles of Life, Light of Life, Nectar of Life, Hugs of Life and Life Without Bugs"). To implement these seven initiatives, BWB would enlist the services of volunteer medical personnel such as: neonatologists, pediatricians, other physicians, nurses, Advanced Registered Nurse Practitioners (ARNPs), respiratory therapists, nutritionists, lactation specialists, pharmacists, pediatric residents, fellows, medical students, and non-medical personnel.

## A Singular Event

The inaugural congress of *Babies Without Borders* will be held in the Fairmont Acapulco Princess Hotel and Resort from September 18-20, 2008. The congress will have three sections: regular conferences, workshops and worktables. The conferences will be given by well-known professors to update the most recent practical advances in the care of sick

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newborns. The academic emphasis will address advances in neonatal resuscitation, respiratory diseases, optimizing nutrition and decreasing infection rates. The workshops will provide an opportunity for the attendees to participate with questions to professors in small friendly groups. In the roundtables the attendees from different regions of the globe will have the opportunity to expose their particular realities, limitations and needs. In this section the volunteers of BWB will have an opportunity to analyze and choose the potential sites where they may help directly or indirectly in the future. This section will serve as a clearing house to match skilled volunteers with towns, hospitals, organizations and individuals who need assistance in developing areas.

Also, the inaugural congress of *Babies Without Borders* distinguishes itself from other academic meetings for its economical impact. Every effort was made to minimize the cost for the attendees, and at the same time, maximize income. The invited professors donate their precious time from their busy schedules to come and share valuable practical information. The Hotel Fairmont Acapulco Princess is graciously contributing not only by significantly reducing their usual room rates in order to maximize congress attendance, but also by donating the use of their salons for all program events. In recent

years the registration fees for high quality academic medical events has increased. BWB is making an effort to maintain the highest standards of continuing medical education while charging a minimal registration fee. The registration fees for physicians, nurses and students are \$120, \$40 and \$30 respectively. This is only a small fraction compared to the fees charged at similar conferences. The ability to have a very low registration fee is due in part to the generous contributions made by the nutritional, pharmaceutical, medical technology companies and medical institutions that are participating in this singular event. All the monies collected will be used to buy equipment and medications that will be donated for the care of babies born in the regions of greatest need.

The Steering Committee of BWB not only will supervise the distribution of the donations, but also will be involved in the "hands on" education that will follow the congress, as well as onsite evaluations that will continue every six months to measure the outcomes.

For more information please see [www.fepece.org](http://www.fepece.org) or contact us at [aesoliz@aol.com](mailto:aesoliz@aol.com) or [BWBSF@aol.com](mailto:BWBSF@aol.com)

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## Medical News, Products and Information

### Prenatal Biochemical Screening Only Detects Half of Chromosomal Abnormalities

Prenatal biochemical screening tests are widely used to look for chromosomal abnormalities in the fetus which can lead to serious handicap, or even death during gestation or in the first few days after birth. But these tests are only able to detect fewer than half of the total chromosomal abnormalities in the fetus, a scientist told the annual conference of the European Society of Human Genetics. On June 2, 2008 in Barcelona, Spain, Dr. Francesca R. Grati, of the TOMA Laboratory, Busto Arsizio, Italy, said that these findings mean that women should be better informed on the limitations of such diagnostic tests.

The researchers studied 115,576 prenatal diagnoses carried out during the last fourteen years. Eighty-four thousand eight-hundred forty-seven were amniocenteses, usually carried out around the 16th week of pregnancy, and 30,729 chorionic villus samplings, which can be undertaken from 12 weeks into the pregnancy.

Both these tests carry an increased risk of miscarriage, so the decision about whether or not to undertake them, can be difficult to weigh. "Since our sample included a large number of women aged less than 35 who underwent invasive prenatal diagnosis without any pathological indication to do so, we felt that the results could be useful in helping to inform pre-test counseling of such women", says Dr. Grati. "Up until now, the information we had come from smaller studies which only looked at the performance of these tests in detecting a limited number of chromosomal abnormalities."

After analysing the results of the chromosomal abnormalities from their own dataset, the researchers combined them with the official detection rates for these abnormalities published by SURUSS and FASTER consortia. These are multi-centre research groups involved in the investigation of screening and diagnostic tests performed in pregnancy, whose results are being used to optimize prenatal care for pregnant patients. They found that current screening procedures were only able to detect half the total chromosomal abnormalities in women both younger and older than 35.

"The TOMA laboratory is particularly suited to carry out this kind of research," says Dr. Grati, "because it was among the first in the world to deal with prenatal diagnosis, and has a vast number of prenatal diagnostic samples at its disposal."

Current tests do not detect all fetal chromosomal abnormalities, but only trisomies 21 (Down Syndrome), 18 (Edward's Syndrome), and 13 (Patau Syndrome), monosomy X (Turner Syndrome), and triploids (conceptuses with 69 chromosomes instead of 46). "These are common vital chromosomal abnormalities, but there are many others which are not picked up by these tests", says Dr. Grati. "And the tests do not even detect 100% of the common abnormalities."

At conception, 23 chromosomes from each parent combine to create a fetus with 46 chromosomes in all its cells. Trisomy occurs when the fetus has one additional chromosome (47 instead of 46). The extra genetic material from the additional chromosome causes a range of problems of varying severity.

In Down Syndrome, for example, where the fetus has three copies of chromosome 21, babies are usually born with impaired cognitive ability and physical growth, cardiac defects and a characteristic

facial appearance. Unlike many other such abnormalities, however, babies born with Down Syndrome are able to lead relatively normal lives and their life expectancy is around 50 years.

Other than trisomy, the fetus can also have the loss of genetic material (deletions) or chromosomal abnormalities in a non-homogeneous form, where there is a mixture of two cell lines, one normal and the other abnormal. "Some of these disorders are relatively common in the fetus, which may have as much chance of surviving as children who are born with Down Syndrome, and it is worrying that current biochemical tests are not always able to detect them" says Dr. Grati. "Our research confirms that it is fundamental for doctors to counsel patients about the limitations of current screening methods, so that they can make an informed decision on whether or not to undergo invasive diagnostic testing."

### 10th Annual Miracle Miles 15K, 5K and Kids' Fun Runs Presented by Chick-fil-A®



*Some of the NICU graduates that were at the 2007 Miracle Mile. Michelle Kendall-Krueger, winner of the women's 15K run eight out of the past nine years, pictured in the center with a runner's bib, number 2826.*

Runners from across Central Florida, the state and Southeast will participate in the 10th Annual Miracle Miles 15K and 5K runs on Saturday, September 27, 2008 at Winnie Palmer Hospital for Women & Babies, 83 W. Miller Street, Orlando. The 15K run begins at 7 a.m. followed by the 5K at 7:10 a.m. A Kids' Fun Run will be held at 9:30 a.m. Proceeds from the event benefit the Neonatal Intensive Care Unit at Winnie Palmer Hospital.

Entry fees through September 20, 2009 are \$25 – 15K; \$20 – 5K; from September 21 – 26, 2008 - \$30 – 15K; \$23 – 5K and day of registration is \$35 - 15K, and \$30 - 5K. The Kids' Fun Run is free. *Miracle Miles* is the third largest 15K Run in Florida, and the largest one in Orlando. For more information, call (407) 896-1160.

"We are very excited about this year's race as the response has been tremendous from both runners and community sponsors," explained Dr. Gregor Alexander, neonatologist, Winnie Palmer Hospital and founding physician of *Miracle Miles*. "We are also grateful for the support of our presenting sponsor – Chick-fil-A. Through their support, and that of everyone involved with *Miracle Miles*, many tiny lives will be saved and forever touched."

More than 1,200 premature babies are cared for every year in the Neonatal Intensive Care Unit at Winnie Palmer Hospital. Many of them go on to lead normal, healthy lives and come back to participate in the *Miracle Miles* event either as a volunteer or participant. One such NICU graduate is Michelle Kendall-Krueger who has won the women's 15K run eight out of the past nine years. She was unable to run in last year's event because she was expecting her first child; however, Michelle is planning to participate again this year.

The 112-bed unit is the fourth largest Neonatal Intensive Care Unit in the country with Level II and Level III beds for the highest level of care for the tiniest, most seriously ill babies. Additionally, it is one of only four in the state to provide Extracorporeal Membrane Oxygenation (ECMO), a heart-lung bypass procedure for babies with severe lung or heart failure.

Winnie Palmer Hospital for Women & Babies, supported by Arnold Palmer Medical Center Foundation, is a 285-bed facility dedicated exclusively to the needs of women and babies. The hospital includes comprehensive fetal diagnostics and labor and delivery services, a regional center for neonatal intensive care, maternal intensive care and women's services. Annually, more than 14,000 babies are born at Winnie Palmer Hospital, making it the busiest labor and delivery unit in the state of Florida. To learn more, visit [www.winniepalmerhospital.org](http://www.winniepalmerhospital.org), or participants can register online through September 25, 2009 at: [www.trackshack.com](http://www.trackshack.com).

### Prenatal Drug Exposure Linked to Sleep Problems in Children

The effects of prenatal drug exposure on sleep, prenatal drug exposure is associated with greater sleep problems in children. In addition, nicotine has a unique effect, and early sleep problems predict later sleep problems, according to a research abstract that was presented at SLEEP 2008, the 22nd Annual Meeting of the Associated Professional Sleep Societies (APSS).

The study, authored by Kristen Stone, PhD, of Brown University in Providence, Rhode Island, investigated reports across time of 139 mothers regarding the sleep of their children - from 18 months to nine years of age. Of these children, 23 had no prenatal drug exposure, 55 were exposed to cocaine alone or in combination with other drugs, and 61 were exposed to drugs other than cocaine.

According to the results, children with prenatal drug exposure - nicotine, alcohol, marijuana, opiates, or some combination of these - experienced greater difficulty sleeping than unexposed children.

Analyses revealed that prenatal nicotine exposure predicted difficulty sleeping above and beyond the other substances. Early sleep problems also predicted later sleep problems.

"Studying the effects of prenatal drug exposure on sleep may provide clues regarding how drugs affect the developing brain and may explain some of the effects of prenatal drug exposure on other outcomes, such as behavior and attention," said Dr. Stone. "For example, studies show that adolescents with prenatal nicotine exposure are more likely to start smoking earlier than their peers, but we don't know what other factors, such as sleep, might be involved in that relationship."

It is recommended that infants (3 to 11 months) get 14 to 15 hours of nightly sleep, while toddlers get 12 to 14 hours, children in pre-school 11-13 hours and school-aged children between 10-11 hours.

The American Academy of Sleep Medicine (AASM) offers some tips for parents:

- Follow a consistent bedtime routine. Set aside 10 to 30 minutes to get the child ready to go to sleep each night.
- Establish a relaxing setting at bedtime.
- Interact with your child at bedtime. Don't let the TV, computer or video games take your place.
- Keep your children from TV programs, movies, and video games that are not right for their age.
- Do not let your child fall asleep while being held, rocked, fed a bottle, or while nursing.
- At bedtime, do not allow your child to have foods or drinks that contain caffeine, or give him/her any medicine that has a stimulant at bedtime, including cough medicines and decongestants.

The value of sleep can be measured by the child's happy nature and natural energy. A tired child may have development or behavior problems. A child's sleep problems can also cause unnecessary stress for parents and the other family members.

### Research Suggests Long-Term Effects of Fetal Cocaine Exposure

Are the estimated 1 million young adults who were exposed to cocaine before birth more vulnerable to drug abuse today? New research indicating long-lasting brain changes suggests the possibility - especially in males - according to a report from Wake Forest University School of Medicine.

At the annual meeting of the American Society of Pharmacology and Experimental Therapeutics in San Diego, CA, (April 7), the scientists reported that adult male monkeys that were exposed to cocaine in the womb appear to have altered function of an important target in the brain, known as dopamine 3 (D3) receptors. In humans, altered dopamine receptor function is associated with increased vulnerability to drug abuse.



### Contemporary Management of Neonatal Pulmonary Disorders Conference

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"This was a unique opportunity to study the possible long-term effects of fetal cocaine exposure," said Lindsey R. Hamilton, a graduate student in the laboratory of Michael Nader, PhD, a professor of physiology and pharmacology. "These animals were exposed to cocaine in the womb 13 years ago and have had little experience with drugs since."

There are five known receptors for dopamine, a chemical in the brain that is similar to adrenaline. Dopamine affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. Drugs such as cocaine and heroin target this reward system by increasing levels of dopamine.

The scientists looked for differences in the dopamine systems of animals that had prenatal exposure to cocaine versus those that had no exposure. Studying D1 and D3 receptor levels was simple -- there are drugs that stimulate the receptors and induce easily observable behaviors such as eye blinking (D1) or yawning (D3).

The researchers saw no differences in the D1 system in the two groups of animals. But, the male monkeys who had been exposed to cocaine yawned almost twice as much during a 30-minute period as males who had no drug exposure.

"This was particularly striking considering that the prenatal exposure was more than 13 years ago," said Hamilton. "It suggests that these animals have either an increased number of D3 receptors or that the receptors have higher function or sensitivity."

Human autopsy studies show higher numbers of D3 receptors in those who have died from cocaine overdose.

To look for differences in D2 receptors, the researchers used positron emission tomography imaging. They found no difference between the two groups of animals. In humans, lower levels of D2 receptors are associated with increased vulnerability to drug abuse.

Next, the researchers will conduct studies in which the animals can self-administer

cocaine to determine whether the males exposed to cocaine in the womb will be more vulnerable to abuse than the other animals.

"Just because there is a difference in the D3 system doesn't mean it will increase their vulnerability to cocaine use," said Hamilton. "Further research will help us answer the question raised by our preliminary research -- whether male children who are exposed to cocaine in the womb may be more vulnerable. It's a timely question both because many who were exposed prenatally are now young adults and because cocaine abuse amongst young women of childbearing age is a growing problem in this country."

The research was funded by the National Institute on Drug Abuse and was part of Wake Forest's Center for the Neurobiological Investigation of Drug Abuse. Co-researchers were H. Donald Gage, PhD, in the Department of Radiology, and Tonya L. Calhoun and Michael A. Nader, both in the Department of Physiology and Pharmacology. For more information, visit [www.wfubmc.edu](http://www.wfubmc.edu).

### **Newborns in ICUs Often Undergo Painful Procedures, Most Without Pain Medication**

An examination of newborn intensive care finds that newborns undergo numerous procedures that are associated with pain and stress, and that many of these procedures are performed without medication or therapy to relieve pain, according to a study in the July 2, 2008 issue of JAMA.

"Repeated invasive procedures occur routinely in neonates [a baby, from birth to four weeks] who require intensive care, causing pain at a time when it is developmentally unexpected. Neonates are more sensitive to pain than older infants, children, and adults, and this hypersensitivity is exacerbated in preterm neonates. Multiple lines of evidence suggest that repeated and prolonged pain exposure alters their subsequent pain processing, long-term development, and behavior. It is essential, therefore, to prevent or treat

pain in neonates," the authors write. "Effective strategies to improve pain management in neonates require a better understanding of the epidemiology and management of procedural pain."

Ricardo Carbajal, MD, PhD, of the Hôpital d'enfants Armand Trousseau, Paris, and colleagues collected data on neonatal pain, based on direct bedside observations in intensive care units (ICUs) in the Paris region. The study, conducted between September 2005 and January 2006, included data on all painful and stressful procedures and corresponding analgesic (a medication used to relieve pain) therapy from the first 14 days of admission collected within a 6-week period from 430 neonates admitted to tertiary care centers. The average gestational age was 33 weeks, and the average intensive care unit stay was 8.4 days.

During the study period, neonates experienced 60,969 first-attempt procedures, with 42,413 (69.6%) painful and 18,556 (30.4%) stressful procedures; 11,546 supplemental attempts were performed during procedures including 10,366 (89.8%) for painful and 1,180 (10.2%) for stressful procedures. Examples of painful procedures that were performed include nasal and tracheal aspiration (removal of fluid), heel stick and adhesive removal. The average number of all procedures per neonate was 141 and the average number of procedures per day of hospitalization was 16. Each neonate experienced a median (midpoint) of 115 procedures during the study period and 16 procedures per day of hospitalization. Of these, each neonate experienced a median of 75 painful procedures during the study period and 10 painful procedures per day of hospitalization.

Infants received specific analgesia for a median of 20% of the painful procedures performed during the study period. Of the 42,413 painful procedures, 907 (2.1%) were performed with pharmacological-only therapy, 7,734 (18.2%) with nonpharmacological-only therapy, 164 (0.4%) with both, and 33,608 (79.2%) without specific preprocedural analgesia.

Further analysis indicated that prematurity, parental presence during procedures,

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neonates undergoing surgery, daytime performance (7 a.m. to 6 p.m.), and day of hospitalization (2-14 days) were associated with greater use of specific pre-procedural analgesia, whereas mechanical ventilation, noninvasive ventilation, and the administration of nonspecific concurrent analgesia were associated with less frequent use of specific pre-procedural analgesia.

"Advances in neonatal care in recent decades with increased survival of immature and sick neonates have led to an increased number of invasive procedures that may cause pain in these vulnerable neonates. The prevention of pain in critically ill neonates is not only an ethical obligation, but it also averts immediate and long-term adverse consequences," the researchers write. "... strategies to reduce the number of procedures in neonates are needed urgently. The American Academy of Pediatrics recently emphasized the need to incorporate a principle of minimizing the number of painful disruptions in neonatal care protocols. Such strategies would aim at bundling interventions, eliminating unnecessary laboratory or radiographic procedures, using transcutaneous measurements when possible, and minimizing the number of procedures performed after failed attempts."

"The knowledge that some vulnerable neonates underwent 153 tracheal aspirations or 95 heel sticks in a two-week period should elicit a thoughtful and relevant analysis on the necessity and the risk-benefit ratio of our clinical practices."

### Better Tools Needed for Assessing Infant Pain

Currently used pain assessment tools may be underestimating the pain response in infants according to a study published in the open access journal PLoS Medicine this week. Dr Slater and colleagues (University College London, UK) studied the association between cortical pain responses in young infants and currently used pain assessment tools which are based on behavioral and physiological measures, such as change in facial expression.

Evidence suggests that inadequate pain management in infants may have immediate and long-term effects. Repetitive pain in preterm infants has been associated with attention deficit disorder, learning disorders and behavioral problems in later childhood.

The researchers studied twelve clinically stable infants on 33 occasions when they required a heel lance for a clinical reason. The relationship between brain activity and a clinical pain score, calculated using the premature infant pain profile (PIPP), was examined in response to this painful event. They found that changes in brain activity correlated to the PIPP scores. These changes were more strongly linked to the behavioral components of the PIPP, e.g., facial expression, than physiological components, e.g., heart rate. They also observed no change in facial expression in 13 of the 33 test occasions, but 10 of these showed a positive brain response.

While this was a small single-centre study on clinically stable infants, the results raise further awareness of the ability of infants to experience pain. And, as the authors say, the results highlight the possibility that "pain assessment based on behavioral tools alone should be interpreted with caution as they could underestimate the total pain response."

Citation: Slater R, Cantarella A, Franck L, Meek J, Fitzgerald M (2008) How well do clinical pain assessment tools reflect pain in infants? PLoS Med 5(6): e129. <http://medicine.plosjournals.org/perlserv/?request=get-document=10.1371/journal.pmed.0050129>

### Guidelines for the Reporting of Health Research are Underfunded

Although reporting guidelines can improve the accuracy and reliability of research reports, there is little funding available for developing such guidelines, according to a new survey published in the open access journal PLoS Medicine this week.

The survey was conducted by the EQUATOR Network ([www.equator-network.org](http://www.equator-network.org)), a new initia-

tive funded by the UK National Health Service. The initiative aims to coordinate the efforts of those developing good reporting guidelines across many areas of medical research, and to provide resources for training and for the promotion of guidelines. Its inaugural meeting was held on the June 26, 2008 at the Royal Society of Medicine, London.

The poor reporting of a medical study's methodology and findings can lead to ineffective treatments, the waste of valuable health care resources and harm to patients. Guidelines such as the CONSORT Statement, a checklist that was developed in 1996 to allow authors to transparently report how a clinical trial was designed, analyzed and interpreted, have led to important improvements in the reliability of published research and how it can translate into practice. But despite the fact that there are now similar reporting guidelines for other types of medical research, including diagnostic and epidemiological studies, their potential is not fully realized. They are not routinely used on a large scale and most journals do not actively promote them (an earlier study showed only 22% of journals included the CONSORT Statement in their guidelines for authors, despite the fact that the statement is widely accepted).

In the EQUATOR Network's first project, Dr. Iveta Simera (of the Centre for Statistics in Medicine, Oxford, United Kingdom) and colleagues from the UK, Canada and the United States, conducted a systematic search to find out how many guidelines there are with the broad objective of improving the reporting of health research. They surveyed the authors of the 37 guidelines that met the researchers' search criteria to establish the motivation behind the development of the guideline in question and to understand the major problems experienced with the guideline's development, update and impact.

Despite the fact that the motivation behind guidelines reflected concern about reporting standards in many fields of medical research, few authors had received dedicated funding for the development of guidelines. Lack of funding and time-constraints were identified as the two ma-



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job problems: often the authors' institutions did not consider the development of reporting guidelines as academic research. The survey found that financial support is needed to help promote guidelines once they have been developed. It also showed a need to harmonize the development of these different guidelines (they must all have a robust methodology to be widely accepted).

"Poor reporting cannot be seen as an isolated problem that can be solved by targeting only one of the parties involved", concludes the survey. "A well-coordinated effort, with collaboration between the research and publishing communities, strongly supported by research funders, will likely have a better chance of leading to improved reporting of health research."

Citation: Simera I, Altman DG, Moher D, Schulz KF, Hoey J (2008) Guidelines for reporting health research: The EQUATOR Network's survey of guideline authors. *PLoS Med* 5(6): e139.

read the online version go to: <http://medicine.plosjournals.org/perlserv/?request=get-document=10.1371/journal.pmed.0050139>

### Tiniest Graduates of Rush Children's Hospital's Neonatal Intensive Care Unit Celebrate Life

Former tiny patients of Chicago's Rush University Medical Center's neonatal intensive care unit (NICU) and their families will reunite with their doctors, nurses and staff at the 34th annual Rush Children's Hospital Premie Picnic. This year's event was held on Sunday, June 22, 2008 at the Armour Academic Center.

Five-time winner of the Chicago Music Awards, Funkadesi, performed at this year's festivities. Along with the live music entertainment, activities included food, games, prizes, and crafts for the children.

"The annual Premie Picnic celebrated the lives of babies and families who have 'graduated' from our special care nursery," said Debbie Gist, RN, Unit

Director of Women's and Children's Nursing at Rush. "All of these babies were in the NICU because they were critically ill and needed 24-hour, comprehensive care."

More than 500 NICU families attend the event each year. Last year, the NICU at Rush cared for more than 500 infants, many who were born prematurely.

"Many of these babies stay with us for months at a time and we get to know the families so well that we feel like we are an extended part of the family," said Jennifer Paulsen, RN, a NICU nurse at Rush.

"Families from throughout the Chicago area, suburbs and from out-of-state came to the annual Premie Picnic. It's wonderful to see a room full of babies and children that have overcome major obstacles and are truly walking miracles," said Gist.

The Rush NICU provides the full spectrum of medical and surgical care for infants born at Rush or transferred from other hospitals. The NICU provides neonatal specialty care including high frequency ventilation and nitric oxide therapy.

All high-risk deliveries, including all pregnancies less than 32 weeks gestation, are attended by a board-certified neonatologist. All critical clinical decisions are made at the bedside by the board-certified neonatologist 24 hours a day.

The NICU receives full subspecialty support from pediatric medical subspecialists, pediatric surgery and other surgical subspecialties. In addition, Rush Children's Hospital is the only hospital with complete neonatal nurse practitioner coverage on all low birth weight infants. These two factors have been associated with lower mortality and morbidity rates.

The unit staff includes neonatologists, neonatal nurses, nurse practitioners and respiratory therapists. Also available are pediatric medical subspecialists, pediatric surgeons and other surgical subspecialties as needed to care for infants in the unit. Go to [www.RUSH.edu](http://www.RUSH.edu).

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- ICD-9 00.12 provides tracking data for payers that may affect current and future reimbursement levels
- ICD-9 00.12 may reduce claims-processing delays associated with miscellaneous HCPCS<sup>a</sup> or CPT<sup>b</sup> codes
- ICD-9 00.12 may trigger contractual payment mechanisms

<sup>a</sup> HCPCS, Healthcare Common Procedure Coding System.

<sup>b</sup> CPT, current procedural terminology.



### Next Steps...

**Contact** your hospital information management group to confirm that they are identifying and coding the administration of inhaled nitric oxide with ICD-9 00.12.

**Reach out** to your local sales representative for additional reimbursement services.

**Call** 1-877-KNOW-INO (1-877-566-9466) to learn more and be put in touch with a national account manager.

**INOtherapy Reimbursement Service: 1-877-KNOW-INO (1-877-566-9466) or [reimbursement@inotherapy.com](mailto:reimbursement@inotherapy.com).**

**INOmax<sup>®</sup>**  
(nitric oxide) **FOR INHALATION**