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I wrote this quickly, while I was still irate. I have submitted enough papers to journals, with sufficient acceptances and rejections to allow myself some emotional distance when I get another rejection. However, I get agitated when both reviewers, anonymous always, fail to understand my thesis and criticize the manuscript for being unfounded. This has been the case on more than one occasion when I’ve attempted to make psychiatrists, few of whom have any interaction with Parkinson patients, aware of their peculiar and interesting problems.

In the latest example I collected a series of fascinating hallucinations, delusions and compulsions described by colleagues around North America to illustrate the spectrum of the phenomenology. The critiques write “old stuff; we know that; it’s well described in the literature on schizophrenia. You should look up the following article, which does a better job of it.” Well, it wasn’t stated exactly like that, but close. What upset me though, was that my article sought to show how different the problem was, and how very much unlike schizophrenia these problems are. To make matters worse, the second reviewer provided a different reference. And to seal the deal, both references were completely unrelated to what all three of us were talking about. It made it clear to me that the reviewers needed some education, and, but I’m unsure how to accomplish this, how to make clear to those in our field how much those outside of it, whom we often rely on for help, don’t know.

The episode also reminded me of a true anecdote. When a close friend was a fellow, he trained with a famous doctor at the Mayo Clinic. Dr Famous came into the lab one day and proclaimed, “I’m so pleased to see that peer review really does work.” He then went on to explain that he had submitted a paper to a major journal in the field and it was rejected. He thought this represented a poor choice of reviewers, and unlike the rest of us, was entitled to a re-review. Because of his fame, and probably a close relationship with the editor-in-chief, he got a re-review, and it was rejected a second time. He then evidently got upset that such a prestigious journal could have done so poorly finding reviewers that he submitted it a third time, at which point it was accepted. As we all teach our children, life’s not fair. Most journals have an iron-clad policy forbidding repeated reviews.

Getting papers published can be a hazardous enterprise for the ego. I’ve had the most trouble in situations, trying, as a neurologist, to publish articles that are largely psychiatric in psychiatric journals. It is impossible to know if the problem is my lack of sophistication in the field, my inability to be adequately critical of my own work in a field that I’m not formally trained in, or whether it’s due to a bias of reviewers trying to maintain an elevated view of themselves that outsiders couldn’t possibly have the expertise to be admitted to their club. In fact, in my own narrow research field, behavioral aspects of PD, the vast bulk of the work, from observational to drug treatment trials, is confined to the neurological literature. Most PD specialists found, very early on, that most of their consulting psychiatrists didn’t know much about PD, and didn’t appreciate their very specific problems and responses to medications so that the clinical studies needed to be published in movement disorder journals in order that the actual treating doctors would be educated. I think that even the few psychiatrists, usually geriatric psychiatrists, who published in this area sought movement disorder forums for the same reason. And, in some sense, this is good because it has expanded the focus of movement disorder specialists to embrace behavior, which is relevant to almost all neurological disorders, especially movement disorders.

I suspect that neurologists and other specialists are equally blind in reviewing outsider (non-neurologist) papers. We all probably, if we think about it, feel the bristles going up on the back of our necks when we see a paper submitted by a non-club member. “How could that doctor have any expertise?”

On the other hand, we are often blind to the things we don’t see or appreciate. We usually lack the expertise and sophistication of different disciplines, but there is a role for bowing to data and observations that have not been made in other fields.

When I receive a rejection like this, I think back to my early days of submitting articles. At some point, after about three or four years, I started getting accepted more often. Considerably more often. I thought this was due to my having joined a clinical research group comprised of most of the famous leaders in the field. I was, of course, quite junior to them, but they were on the editorial boards of journals, published many important articles, and reviewed most of the papers in our field. I was now a “member” of the club. I discussed this with one of that group’s distinguished but younger members and told him that I thought that I was now getting accepted because the people reviewing my papers now knew me and probably either had a lower threshold or were more likely to believe my reports. He disagreed and thought that, with experience, I had simply learned and improved and was submitting better papers.

Of course, I still don’t know who was correct. Probably both of us, and I’ll never know. In the meanwhile I’ve asked a psychiatrist-friend to review my latest rejection and tell me if I’m paranoid or justified. She’s a psychiatrist who works with neurologists and I’m a neurologist who works with psychiatrists. She calls me the “reverse” her. I like that and will persevere as we both aim towards further integrating our disciplines. Parochialism only serves the past.

— Joseph H. Friedman, MD

Disclosure of Financial Interests
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Long before there had been clinical thermometers there were humans burdened with fever expressing itself as copious sweat upon a burning forehead. But not all fevers were the same: there were fevers that did not abate but seemed to consume the body; there were fevers of the brain causing frenzied delirium; and fevers thought to be so deeply seated that they must be infiltrating the bones; and fever so profound that no febrifuge could offer relief. Truly, in the words of Thomas Sydenham (1624-1689), fever is Nature’s way of expressing its terrible distemper. And if the body ever needed to publish an autobiography of its dysfunctions surely it would express itself through a fever’d brow and a temperature chart.

There are few terms in English so expressive of deep feelings as the word, fever, and yet so ambiguous that it can be employed as a metaphor for the entire spectrum of human passions. The word, fever, has been used liberally—one might say, feverishly—by physicians, by Victorian poets and by those enthralled by life’s many temptations and compulsions.

Physicians had been ill-equipped to understand those ailments accompanied by the sundry fluxes, fevers and frenzies that assail human life; and so they gave scholarly names to those vexing ailments associated with heated human bodies. And thus there was spotted fever, gaol fever, puerperal (childbirth) fever, ship fever, tertian fever, quotidian fever, quartian fever, river fever, swamp fever, sweating fever, yellow fever, blackwater fever and a thousand separate fevers bearing geographic names such as Crimean fever or Mediterranean fever. Physicians further divided fevers into those accompanied by skin changes; and thus there were poxes, exanthems, macular rashes, papular rashes and even confluent rashes. Yet with all of the proliferation of names, there was not a single systemic fever that had responded to any medical intervention other than common sense measures such as bed rest and fluids by mouth. Sixteenth Century physicians, confronted with a variety of fevers, viewed them as a Martian might struggle to understand a major league baseball game, assuming that the outer numbers on the uniforms would somehow provide an adequate explanation.

Both philosophers and physicians agreed that fever was a puzzle; but the philosophers went further by announcing that fever was merely the primal substance of life announcing itself to the observer. After all, they declared, when life departs, does not the body warmth also depart? Some fever, then, was deemed a necessary, normal, component of that divine intervention, that fragile spark called life. And so it was concluded that an excessive fever was but an overt human response to the Creator’s touch; and if it was feverishly exuberant, it then represented a visceral conflict between combating cosmic forces played out in the amphitheater of the human body. To suppress or abort fever, then, represented an ill use of man’s meager resources. It remained for a small minority of skeptical physicians to consider fever, alternatively, as an unrequited intrusion of the human substance by an unwanted invader. Some sought remedies to lower the fever while others, nihilists in spirit, believed that with time fevers will eventually burn away. William Osler (1849 – 1919) stated: “Humanity has three great enemies: fever, famine and war; and of these by far the greatest, by far the most terrible, is fever.”

Poets thought that fevers were the body acknowledging the presence of anguish and dismay. Keats (1795 – 1821) wrote:

Fade far away, dissolve and quite forget
What thou among the leaves hast never known,
The weariness, the fever and the fret
Here where men sit and hear each other groan:
Where palsy shakes a few sad, last gray hairs,
Where youth grows pale and specter-thin and dies.

And Dylan Thomas (1914-1953), in a different century, carrying the metaphor of fever far beyond the precincts of medicine or customary passions, thought of the bloody, feverish consequences when bloodless statesmen signed great treaties:

The hand that signed the treaty bred a fever,
And famine grew and locusts came;
Great is the hand that holds dominion over
Man by a scribbled name.

Dylan Thomas’ fevers were of the nonpyretic type with the burning confined to the inner soul. Such a fever had a companionship with the gamblers’ fever and the other negative but febrile compulsions of life.

Macbeth called life but a fitful fever. W.H.Auden (1907-1973) agreed declaring that “not to be born is the best for man”, but Boris Pasternak (1890-1960) who knew something of wintry fevers in the gulag, advised otherwise: “To live life to the end is not a childish task.”

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Disclosure of Financial Interests

Stanley M. Aronson, MD, and spouse/significant other have no financial interests to disclose.

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We all heard this in medical school and, given that common things occur commonly, it is, generally, excellent advice. But even in little Rhode Island, conditions with an annual incidence of one in 100,000 will occur ten times a year. The Children’s Neurodevelopment Center at Hasbro Children’s Hospital is a multidisciplinary center, which includes the subspecialties of: child neurology, developmental-behavioral pediatrics, genetics, metabolic disorders, neuro-rehabilitation, newborn screening, orthopedics, psychology, sleep medicine, urology. The center provides care for children with relatively common disorders, such as ADHD, sleep disorders, epilepsy, cerebral palsy, autism, developmental disabilities, and also offers the expertise to track down zebras.

This issue is devoted to the zebras, which, while rare, highlight the advances being made in our understanding of normal physiology and the pathophysiology of disease.

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Rhode Island Metabolic Newborn Screening: The Effect of Early Identification. A Case Report of Argininosuccinic Aciduria (ASA)

Natalie M. Beck, MGC, CGC, Julie Pocost Johnston, RD, LDN, Karen S. Lemke, RN, BSN, Peter Pogacar, MD, and Chanika Phornphutkul, MD

Starting from a single metabolic disorder in 1962, newborn screening (NBS) has expanded from identifying persons with phenylketonuria (PKU), to a national division of the public health system and includes metabolic conditions, hemoglobinopathies, endocrinopathies, infectious diseases, congenital hearing loss and cystic fibrosis. Modern technological advancements, such as tandem mass spectrometry (MS/MS), have allowed for a higher volume of samples to be accessioned for an increasing number of conditions with better accuracy and in a more timely manner. This advanced system still utilizes the original style of specimen, the ‘Guthrie specimen’ of dried blood spots on filter paper. With MS/MS, a single assay from a sample of this blood spot allows for screening for many inborn errors of metabolism.

Screen positive results can be deemed ‘true’ or ‘false’ after additional testing. The majority of positive results are eventually found to be ‘false positive NBS’ which can result from transient abnormalities due to neonatal physiological analyte variation, transient enzyme immaturity in preterm infants, iatrogenic factors, medications such as antibiotics, or maternal diet or medical conditions. This is usually determined by obtaining a new specimen and running a second MS/MS NBS. For more suspicious screen positive results, additional analyte levels can be assessed and second tier testing can be done on the original Guthrie filter paper blood spot, which improves the specificity of NBS and decreases the time for the infant to receive directed follow up care. Examples of these include the automatic molecular testing of common mutations for infants who are screen positive for galactosemia or cystic fibrosis.

To provide more comprehensive and standardized newborn screening throughout the country, the American College of Medical Genetics (ACMG) and the United States Health Resources and Services Administration recommended a uniform panel of 29 disorders for what is now called ‘expanded NBS’ in 2006. At present, nearly every infant born in the country is screened for over 30 conditions in a standardized fashion, independent of the state of birth. While each metabolic condition included in NBS is quite rare (ranging in prevalence from one in 5,000 to less than one in 200,000), the incidence of a newborn to have any of these collectively is approximately one in 4,000 births. Early 21st century investigations revealed that even with only some states in the New England region utilizing expanded metabolic NBS, there was already over a 30% increase in affected infants being identified. Over six years later, this number has grown. The state of Rhode Island adopted the expanded NBS in July 2006.

All of the conditions that are part of metabolic NBS are chronic, requiring lifelong treatment and management. NBS allows for early identification of affected infants prior to clinical presentation and for implementation of treatment(s), to prevent or reduce symptoms of these disorders, which can include, but are not limited to: developmental delay, mental retardation, alopecia, ataxia, seizures, memory problems, metabolic acidosis, hyperammonemia, coma, and in some cases, death. In this article, we report a newborn with a urea cycle defect which was detected by NBS. Diagnosis was confirmed and treatment was instituted prior to the infant becoming symptomatic.

Case Report

A boy was born at 40 weeks by vaginal delivery to a G1P0 mother following a pregnancy complicated by intrauterine growth restriction (IUGR), bilateral hydronephrosis and mild hypospadias, weighing 5lbs 12oz (2.6kg). NBS specimen collection was obtained on day two of life. Four days after specimen collection, the NBS co-coordinators were notified of a sample showing increased argininosuccinic acid of 47.64 and an increased citrulline level of 73.39. This pattern was suggestive of argininosuccinic aciduria (ASA), a disorder of the urea cycle.

On day of life seven, the patient was alert and had a normal examination, however his plasma ammonia was elevated at 134 µmol per liter. The patient was treated for hyperammonemia using a combination of sodium benzoate and sodium phenylacetate (Ammonul®) to reduce ammonia levels, arginine hydrochloride, IV dextrose solution and was made n.p.o. Metabolic laboratory evaluations for the biochemical diagnosis of ASA included plasma amino acids, urine organic acids, plasma ammonia level, electrolytes and glucose level. The results confirmed a biochemical diagnosis of ASA. Due to initial insufficient oral intake during hospital admission, a nasogastric (NG) tube was inserted to ensure appropriate feeds until the infant could maintain proper oral intake. NG tube was discontinued at around two weeks of age. The infant continues to be well-managed at home on a calculated low protein diet of medical formula supplemented by pumped breast milk and arginine supplement. Molecular diagnosis confirmed the biochemical diagnosis of ASA with two previously reported disease-causing mutations: c.1045_1057del13 (p.V349fs) and c.1135C>T (p.R379C).

The patient is growing adequately, and is developmentally appropriate for his age.

Overview of ASA and the Urea Cycle

ASA, also known as argininosuccinate lyase deficiency (OMIM#207900), is a rare autosomal recessive disorder of the urea cycle. The homozygous loss of function of the argininosuccinate lyase (ASL) gene at 7cen-q11.2 leads to insufficient enzyme activity for proper metabolism of excess...
nitrogen, in the form of ammonia, to be converted into urea for excretion. There are five main enzymes of the urea cycle with an important sixth that provides a necessary co-factor for the initial reaction of the cycle (Figure 1). As depicted in the figure, ASL is the fifth enzymatic step in the cycle. With insufficient or absent function of the argininosuccinate lyase enzyme, argininosuccinic acid and citrulline accumulate in the blood and argininosuccinic acid is excreted in the urine. In addition to nitrogen metabolism, the urea cycle is responsible for the synthesis of arginine to supplement dietary arginine. In persons with ASA, this synthesis is prevented, causing arginine to become an essential amino acid.

Clinical presentation of ASA patients can vary greatly. Severe presentations often result in neonatal death, while others with ASA may only have symptoms during illness or other times of environmental stressors. The clinical features of ASA can include: lethargy, vomiting, hypothermia, hyperventilation, hepatomegaly, progressive encephalopathy, seizures, coma, and death. These symptoms all stem from rising ammonia levels in the blood and the brain. Since there is no alternative pathway for ammonia in the body, it can elevate in concentration rapidly in patients with urea cycle defects. During hyperammonemic episodes, ammonia climbs to toxic levels, causing central nervous dysfunction and disturbances in cerebral metabolism, neurotransmitter systems, membrane potentials, pH, protein expression, calcium signaling, and mitochondrial functions, among other problems.

Studies have examined the difference in outcome for patients with metabolic conditions identified by NBS compared to those who present clinically. Significant differences were found in favor of those identified pre-symmetrically by NBS, with lower instances of cognitive, behavioral and motor deficits. Other factors that significantly influenced long term outcome include the prevention of hyperammonemic crises and the age at first hyperammonemic episode.

Dietary management for patients with ASA is similar to those with other urea cycle defects. A protein-restricted diet will prevent excess nitrogen from entering the urea cycle and therefore prevent the resulting elevated ammonia. A standardized level of protein prescribed for this diet is based on weight and age. Protein intake should allow for proper growth and prevent the body from entering catabolism—which produces nitrogen from stored protein. In children who frequently refuse feedings, are recurrently ill or have decreased intake, the placement of NG or gastrointestinal tubes may be necessary for proper intake for a period of time. Arginine supplementation is the second component of the medical diet for persons with ASA, as their bodies are unable to synthesize de novo arginine. Patients who maintain their prescribed medical diet and seek medical attention in times of illness to prevent metabolic crises are expected to have normal outcomes.

**Newborn Screening in Rhode Island**

In the US, every state performs metabolic NBS, however until recently the panel varied greatly. Rhode Island implemented the ACMG-recommended expanded panel in July 2006, and it remains the standard metabolic screen. The state of Rhode Island benefits from its concentrated and multidisciplinary professionals who respond to positive metabolic NBS results. This team includes newborn screening co-coordinators, metabolic and genetic specialists, nursing staff, a genetic counselor, and a dietician specializing in the dietary needs of individuals with metabolic conditions. Our state’s metabolic screening co-coordinators notify the primary care provider of the positive screen and the necessary follow up testing, and then notify the patient’s parents/caregivers of the same. Based on the screen and/or follow up testing, patients are referred for further evaluation and management. A larger group of providers participate in the management of patients with true positive NBS results, including early intervention programs, developmental pediatricians, neurologists, gastroenterologists, physical/occupational/speech and language therapists, case managers, pharmacists, social workers and language interpreters. A key component of this multidisciplinary team is the patient’s pediatrician, who must be familiar with the conditions included in metabolic NBS, as well as their presenting clinical features. For newborns discharged home soon after birth, the pediatrician is most likely to respond to early symptoms of metabolic disease in the first days of life, before NBS results are available. Some resources that may benefit pediatricians and other aforementioned providers are listed in Figure 2.
3. Garg U, Dasouki, M. Expanded newborn screen-
2. Marsden D, Larson C, Levy H. Newborn 
1. Sahai I, Marsden, D. Newborn screening.

**CONCLUSIONS**

The nationwide standardized expanded NBS affords physicians and families the opportunity to identify individuals affected by rare inborn errors of metabolism and intervene before clinical symptoms develop. A well-designed and specific protocol in each state/region allows for notification of positive newborn screen results and the necessary follow up to occur appropriately. After identification, infants with these metabolic disorders require specific treatments and life-long multidisciplinary medical management. This case exemplifies the benefits that a timely and well-coordinated metabolic NBS program provides to infants with positive newborn screen results.

**REFERENCES**

Genetics in Autism Diagnosis: Adding Molecular Subtypes to Neurobehavioral Diagnoses

Helen M. Johnson, John Gaitanis MD, and Eric M. Morrow, MD, PhD

INTRODUCTION: AUTISM GENETICS RESEARCH HAS DIRECT RELEVANCE TO THE CLINIC

Autism is a heterogeneous neurodevelopmental disorder that affects people of all races, ethnicities, and backgrounds and is about four times more prevalent in males.¹ ³ The incidence of autism has risen so dramatically over the past few decades that this increase has been termed the “autism epidemic.” A recent surveillance study reported a 57% average increase in the number of autism diagnoses in specified regions of the United States from 2002 to 2006, and estimated the current prevalence to be one in 110 children.⁴ The increase in diagnosis can be at least partly attributed to greater awareness, broader diagnostic criteria⁵ ⁶ and improved services for autistic children.⁷ Regardless, more children than ever are in need of proper diagnosis, treatment and services for autism.

This article focuses on recent progress in genetic studies relevant to autism diagnosis. This progress has highlighted the genetic heterogeneity of autism, which mirrors the variation in clinical presentation of behavioral symptoms. Genetic research has recently revealed that about 10% of autism diagnoses can be subtyped according to genetic abnormalities.¹ Genetic testing has, therefore, entered the clinical arena. As the multiple genetic etiologies of autism continue to be elucidated and as molecular genetic testing becomes more widely available and less expensive, genetic subtyping of autism will become more common.

DIAGNOSING AUTISM: THE UTILITY OF GENETIC SUBTYPES

In the United States, autism is primarily diagnosed on the basis of characteristic behaviors outlined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).¹ These behaviors include aberrant social interaction, impaired ability to communicate through both verbal and nonverbal means, repetitive behaviors, and obsessive tendencies or fixations. DSM-IV-TR lists five disorders under the umbrella term Autistic Spectrum Disorders (ASDs): Autistic Disorder, Asperger’s Disorder, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), Rett’s Disorder, and Childhood Disintegrative Disorder (http://www.cdc.gov/ncbddd/autism/hcp-dsm.html). These disorders are distinguished by age of onset, specific behaviors, and severity. Rett’s Disorder is the only ASD with a known genetic cause: it is an X-linked, Mendelian disorder caused by mutations in the MECP2 gene.¹⁰

Because diagnosis of autism is based on clinical symptoms, a diagnosis does not necessarily reveal information about the biological cause. Furthermore, clinical symptoms alone may not be sufficiently informative to guide prognosis or treatment stratification. Genetic testing is now linking behavioral diagnoses to genetic loci. Distinct genetic subtypes provide a greater degree of biological explanation for patients and families, and as such may facilitate identification of medical co-morbidities or clinical outcomes. Additionally, diagnostic genetic tests are of great benefit because they may allow for earlier, more accurate detection of autism in young children. Data suggest that the earlier a child begins treatment for his or her autistic symptoms, the greater the chance that the symptoms will diminish;¹² however, it can be difficult to make a clinical diagnosis earlier than two years of age because many characteristic behaviors are related to the acquisition of language and social skills.¹¹

THE GENETIC ARCHITECTURE OF AUTISM: EVIDENCE FOR NUMEROUS, INDIVIDUALLY RARE GENETIC CHANGES

Data from sibling and twin studies provide strong evidence of genetic heritability greater than 90%.¹², ¹³ In light of this, numerous studies have been conducted to identify autism-associated loci and candidate genes. Chromosomal abnormalities have been observed in about three to five percent of autism cases, with abnormalities in the 15q11-13 locus accounting for about one percent of cases.¹³ ¹⁴ G-banded karyotype analysis has been a standard method for detecting autism-associated chromosomal abnormalities for about 35 years. This microscopic analysis of the 46 chromosomes can reveal large chromosomal rearrangements, deletions, and duplications as small as 3 Mb, although it is not uncommon for 5-10 Mb abnormalities to go undetected.¹⁵ Recently, submicroscopic cytogenetic abnormalities have been investigated via microarray-based comparative genome hybridization (array-CGH) studies.

Arguably, the most significant findings of array-CGH studies relate to copy number variants (CNVs): genomic regions larger than 1 kb harboring insertions, deletions, duplications, or more complex variations. Although CNVs are a common form of genetic variation, some—including those in the 15q11-13 locus—are observed more frequently or exclusively in autistic individuals.¹⁴, ¹⁶ The majority of autism-associated CNVs are rare, with the most common recurrent CNVs accounting for at most two percent of autism cases and the least common occurring within a single family.¹⁷ Many of these CNVs are de novo, while others are inherited. Notably, autism-associated CNVs do not appear to act in a Mendelian fashion, in contrast to most classic genomic disorders.

To date, a large number of individually rare genetic changes—including MECP2 mutations and numerous CNVs—have been associated with autism. Because genetic testing with microarrays has entered the clinical lab and because there are novel high-throughput sequencing technologies under active research, these insights have important diagnostic relevance, which is well exemplified by the case below.
**Autism and the 15q11-13 Locus: A Case**

CB is a 16-year-old girl whose first developmental concerns arose at four to five months of age. At that time, she was not visually fixing on faces. She did not smile responsively or laugh. She remained extremely quiet through her first year of life, with only minimal babbling. Language did not develop until approximately three years of age. Rather than go through a period of babbling, she exhibited echolalia. She was able to pronounce words clearly, but did not use them in an appropriate context.

CB engaged only in solitary play until she was approximately three years old, when she began to interact with her older sister. It was not much later that she began to interact with her parents. She did not exhibit joint attention until nine years of age. Even after she began interacting, her play was repetitive. She was very rigid in her behaviors and craved structure. CB had poor attention. She developed simple motor tics including throat clearing. She displayed features of sensory integration disorder; she did not allow anyone to touch her hands and there were certain textures of food that upset her greatly. Over time, CB displayed severe obsessive compulsive symptoms. She has never had any seizures.

The family history was limited since the patient was adopted, but her biological mother was known to have cognitive delays and social impairments. The patient has a half sister by the same mother who has a seizure disorder, cognitive delays, and social impairments.

The physical examination was notable for short stature and almond-shaped eyes. She was otherwise non-dysmorphic. The neurological examination was notable for pressured, perseverative speech involving a limited array of topics. She repetitively asked the same questions and dictated the topics of conversation. CB exhibited poor attention, motor tics, and obsessive compulsive behaviors. She insisted that the examiner use the same stethoscope that had been used during previous visits and that the order of the examination not deviate from previous visits. The remainder of the general and neurological examinations was normal.

To evaluate CB’s developmental concerns, she underwent fluorescent in-situ hybridization (FISH) of the 15q11-13 region. This revealed a duplication within 15q12.

The 15q11-13 locus is highly unstable and subject to genomic imprinting. Of 58 CNVs observed in this locus, 45 are associated with disorders, including Prader Willi Syndrome, Angelman Syndrome, autism, intellectual disability, and schizophrenia. A number of genes within this locus, such as UBE3A and members of the GABA receptor gene family, are expressed throughout the central nervous system and have been associated with autism or other neuropsychiatric disorders.

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More widespread use of genetic testing for autism would enable earlier detection and therefore intervention in a sizable fraction of patients.

Variations at the 15q11-13 locus are observed in up to one percent of autistic individuals, and the majority of the numerous observed variations are maternally-inherited duplications. Many of CB’s symptoms are in accordance with those described in other patients harboring 15q11-13 duplications, including developmental delay, echolalia, lack of major facial dysmorphism, and short stature.

As expected, many of CB’s symptoms overlap with ASD symptoms, including delayed development of language, abnormal social interaction, solitary and repetitive play, sensory integration differences, and strong desire for structure. Based on the family history, it is likely that both CB and her half-sister inherited the duplication from their mother.

Of note, a recent physician advisory (http://www.idic15.org/PhysicianAdvisory_Feb2009.pdf) warns that medications that target the GABA-A receptor—including benzodiazepines, phenobarbital, and ethanol derivatives—may increase the risk of sudden death in individuals with 15q11-13 duplications. Further research is necessary to definitively establish a link between these medications and sudden death in these individuals; however, the fact that the 15q11-13 locus includes several GABA receptor genes provides biological plausibility for this clinical concern.

In summary, CB now has a diagnosis of “autism associated with 15q11-13 duplication.” This molecular subtype of autism provides a biological explanation, has relevance to recurrence risk, may have significant implications for treatment (e.g., caution in prescribing benzodiazepine, phenobarbital, or ethanol derivatives) and may help predict the clinical course.

**Diagnosis in the Multidisciplinary Clinic: The Advantages of Genetic Testing**

Given the wide spectrum of autistic phenotypes, it is fitting that diagnosis and management of this complex disorder is becoming increasingly collaborative. It is common for patients to be seen by a number of professionals, including pediatricians, psychiatrists, neurologists, medical geneticists, and speech and behavioral therapists.

A crucial collaboration is that between clinicians and research geneticists. Although autism remains a behaviorally-defined disorder in DSM-IV-TR, approximately ten percent of ASD cases have known cytogenetic causes and more discoveries are certainly on the way, thanks to the advent of array-CGH technology and the rapid advancement of the field. Discovery of the genetic causes of specific forms of autism will allow these molecular subtypes to be added as descriptors of the behavioral diagnosis, much in the way that MECP2 mutations in Rett’s disorder have provided important biological explanations.

More widespread use of genetic testing for autism would enable earlier detection and, therefore, intervention in a sizable fraction of patients. The benefit of early diagnosis and intervention is highlighted by experiments involving animal models of the monogenic disorders Fragile X syndrome and Rett Disorder, in which early treatment was shown to delay or prevent the onset of autistic symptoms, as well as decrease their severity.

Genetic testing has additional advantages. Firstly, identification of genetic causes of autism not only provides bio-
logical explanations for families but also may help to reduce the stigma around this disorder and prevent the development of false, damaging explanations for autism. Secondly, a specific genetic diagnosis may reveal information important to a patient’s medical future, such as increased risk of sudden death for 15q11-13 duplication patients being treated with GABA-A agonists (http://www.idic15.org/PhysicianAdvisory_Feb2009.pdf) or increased susceptibility to cancer for individuals with PTEN mutations. Thirdly, given the high risk of autism recurrence among siblings, a specific genetic diagnosis in one individual may aid in the identification of autism or related neuropsychiatric disorders such as epilepsy, and/or associated susceptibilities to diseases such as cancer in family members.

A recent consensus statement proposed that microarray analysis should replace G-banded karyotype analysis as the standard genetic test for autistic patients. This recommendation is based on the fact that microarrays have a resolution more than ten times that of karyotypes as well as a diagnostic yield about six times greater. Furthermore, the cost of microarray testing is lower than that of karyotype analysis.

As the cost of genetic testing decreases and clinical microarrays become more widely available, this technology will almost certainly become a standard aspect of autism diagnosis. As we continue to identify the genetic causes of the numerous subtypes of autism, more and more people on the spectrum can benefit from genetic testing, earlier diagnosis, and earlier intervention. Appreciation of the multidisciplinary nature of autism will enhance the rate of discovery of autism-associated loci and facilitate improved diagnosis and treatment of autistic patients, thus improving the lives of individuals and families affected by autism. While progress in autism genetics has made significant contributions to the clinic, much research remains to be done.

References

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**Case Presentation**

NG presented at four years of age with two generalized convulsive seizures, each lasting approximately two minutes, on two consecutive days. His EEG was diffusely slow, but with no epileptiform activity. After a third seizure on the following day he was started on oxcarbazepine. Shortly after starting oxcarbazepine he began having generalized, non-convulsive seizures, which were attributed to the oxcarbazepine, and was switched to levetiracetam. The non-convulsive seizures persisted and were refractory to high doses of levetiracetam, and he was switched to zonisamide, still without control. He was diagnosed with Doose Syndrome and was hospitalized two months after his initial presentation for management of intractable, non-convulsive seizures. The EEG revealed frequent, three-cycle per second, spike-wave discharges with clinical and subclinical seizures. Treatment with valproic acid (VPA) failed to control the seizures; his ammonia (NH3) level became elevated with normal liver function tests (LFTs) and the VPA was discontinued. He had a dramatic response to high dose (1 mg/kg) oral diazepam with normalization of the EEG and complete control of the seizures, and was discharged on zonisamide. However, within days he had a recurrence of the non-convulsive seizures, this time refractory to high dose diazepam. He was hospitalized and treated with ethosuximide. Due to persistent clinical and electrographic seizures, VPA was tried a second time; the NH3 remained in the fifties and there were no changes in the LFTs, but he developed a significant encephalopathy, manifesting with marked somnolence, without control of the seizures. The VPA was discontinued with resolution of the encephalopathy (with one rather disconcerting exception; he emerged from the valproate-induced encephalopathy a Yankees fan, having previously been a dedicated member of the Red Sox nation). Rufinamide was added to his AED regiment and the ketogenic diet was initiated. There was no benefit from the rufinamide, which was discontinued. The child had difficulty tolerating the ketogenic diet, becoming quite nauseated when acidicotic, to the point of requiring NG tube feeding for adequate nutrition. Addition of bicarbonare to his diet resolved the severe acidosis. Levo-carnitine was then added. There was a dramatic improvement in the EEG and complete cessation of clinical seizures. NG’s mental status was back to baseline, though there was a report of a need for a daytime nap. After tapering the zonisamide and ethosuximide, with complete seizure control on the ketogenic diet alone, the daytime lethargy resolved. He developed a better tolerance for the diet and was taking all his nutrition by mouth, without difficulty. After quite a few months he was, again, a Red Sox fan.

**Doose Syndrome**

Myoclonic atactic epilepsy (MAE), also known as Doose Syndrome, was classified by the International League Against Epilepsy, based on the seizure type, as one of a group of cryptogenic or symptomatic generalized epilepsies and syndromes. A subsequent task force on classification terminology of epilepsy syndromes re-classified MAE as a generalized epilepsy, distinguishing it from Lennox-Gastaut Syndrome, Severe Myoclonic Epilepsy of infancy (SMEI or Dravet Syndrome) and Atypical Benign Partial Epilepsy/Pseudo-Lennox Syndrome (ABPE/PLS), with the latter classified as epileptic encephalopathies. The distinction between the different generalized, myoclonic epilepsy syndromes was based on the conclusion that, in cases of the epileptic encephalopathies, the epileptiform abnormalities contribute to the progressive disruption of brain function, whereas MAE has a course that is highly variable, with instances of complete remission of the epilepsy and normal cognitive development.

The EEG findings in MAE are typically primarily generalized spike and wave activity. MAE, as well as SMEI, can present with obtundation due to nonconvulsive status. The cognitive outcome appears to be dependent on whether the epilepsy resolves. MAE is considered an idiopathic generalized epilepsy syndrome, as opposed to the epileptic encephalopathies, which are considered cryptogenic or symptomatic. Prior to the onset of epilepsy, usually between 18 and 50 months of age, children with MAE have normal development. The initial seizure types consist of myoclonic, atactic seizures; ongoing seizures include generalized convulsive seizures, absence seizures, and, less often, tonic and febrile seizures. Medications reported to be beneficial in MAE include: valproate, lamotrigine, ethosuximide and benzodiazepines (all of which, with the exception of lamotrigine, were tried in our case, without persistent control of the seizures). The variability in the choice of treatment and prognosis between the different myoclonic epilepsy syndromes warrants careful attention to correctly classifying children presenting with myoclonic seizures.

**History of the Ketogenic Diet**

Fasting as a method to control seizures has been recognized since at least 500 B.C. The first ‘modern’ use of fasting for the treatment of epilepsy was reported by Guelpa and Marie in 1911. The impracticality of fasting led to the development of the ketogenic diet (KD), described by Wilder in 1921, an effort to mimic the metabolic effects of fasting, yet more tolerable and sustainable. The diet, high in fats and low in carbohydrates, has been utilized with little variation since.

Over the next twenty years, the KD grew in popularity and was a recognized treatment for epilepsy. However, the development and introduction of antiepileptic drugs in the United States resulted in diminished use of the diet. In 1993, a 20-month old boy, Charlie Abrahams, was treated with the KD for intractable complex partial seizures after the failure of multiple AEDs and surgery. Within days of the initiation of the diet, the seizures...
were completely controlled. Charlie's father, Jim Abrahams, created The Charlie Foundation to promote research, awareness and availability of the KD.

Over the last sixteen years there has been an enormous growth of interest in the KD. The KD is now available in over 50 countries and in all continents except Antarctica; and is available at most major medical centers. The KD has become a well-established treatment, supported by extensive research, for the treatment of certain medically-refractory epilepsies

**Proposed Mechanisms of Action**

The KD has been used successfully to treat a variety of epilepsy syndromes, of known and unknown etiology, including Infantile Spasms, Lennox-Gastaut Syndrome, Landau-Kleffner Syndrome, myoclonic-astatic epilepsy (Doose and Dravet Syndromes) and has been successful in epilepsy attributable to genetic syndromes such as Tuberosclerosis, and Rett Syndrome. Yet, in spite of the duration and widespread nature of its use, relatively little is known about the mechanism behind its efficiency. The diet's ability to treat a diverse range of epilepsy syndromes suggests that it may have multiple mechanisms of action, each of which may be more relevant to a specific disease state. In the case of glucose-transport disorders, when glucose cannot be transported across the blood-brain barrier, the generation of ketones, which can be used by the brain as an energy source, provides an alternative fuel source for the CNS. It has been proposed that ketone bodies may serve a similar function in other neurodegenerative disorders.

A study by Oguni et al. compared the response of myoclonic astatic epilepsy to the KD vs. medications. In this study, the KD was the most effective treatment modality, eliminating myoclonic and astatic seizures in fifteen of 26 patients. Medications with GABAergic actions were not as successful as the diet in this study; ACTH and ethosuximide were moderately effective. The greater success of the KD suggests the diet is not merely acting as a GABA-ergic agent in MAE. The relative success of the KD compared to ACTH indicates that the mechanism is something other than a hormonal effect, however, given that the mechanism of action of ACTH is also not understood, this does not add to our understanding of the mechanism of action. Further comparisons of the KD and medications with known mechanisms of action may help better the understanding of the mechanism of action.

**Efficacy of the Ketogenic Diet**

Early studies reported a 75-90% reduction in seizures with the KD. More recent publications, involving larger subject populations, have not confirmed this level of response. When compared to the vagus nerve stimulation, another non-pharmacologic treatment for intractable epilepsy, the KD appears to work more quickly, usually within two to four weeks compared to several months.

Four meta-analyses of the efficacy of the KD provide compelling evidence for benefit of the KD, despite the lack of blinded, controlled trials. In 2000, Lefevre and Aronson reviewed 11 studies and found a 56% responder rate (more than 50% reduction in seizures), 32% of whom had more than 90% reduction in seizures. They concluded, “although controlled trials are lacking, the evidence is sufficient to determine that the ketogenic diet is efficacious in reducing seizure frequency in children with refractory epilepsy.” In 2003, Levy and Cooper reviewed 14 studies, and concluded, “for those with a difficult epilepsy on multiple antiepileptic drugs, we consider the ketogenic diet a possible option.” In 2006, a meta-analyses of 19 studies, encompassing a total of 1,084 patients, found that the KD reduced seizures by more than 90% in a third of the patients and by more than 50% in half. There was no clear evidence of an effect of age, seizure type, or etiology on seizure reduction.

In 2008, a clinical trial by the Institute for Child Health in London by Neal and colleagues, randomized children to start the KD, after either a one-month (treatment group) or four-month delay (control group), with no additional changes in AEDs. The seizure frequency after four months was significantly lower in the 54 children on the KD (38% decrease in seizures), compared to the 49 controls (37% increase in seizures; p < 0.0001). The control group had no children with a greater than 90% reduction in seizures, compared to five children on the KD (P=0.06).

The KD is a promising therapy for MAE, with over half of children showing a greater than 50% reduction in seizures, and 18% achieving seizure-freedom. In drug resistant MAE, the diet should be considered early in the disease course.

**Initiation of the Ketogenic Diet**

Upon determination by the neurologist that a patient may be a candidate for the KD, a registered dietitian with expertise in the diet should be consulted to review the child’s growth history, dietary intake, fluid adequacy, evaluate complicating factors (swallowing and/or chewing difficulties, history of kidney stones, dyslipidemia, liver disease, failure to thrive, gastroesophageal reflux, constipation, cardiomyopathy, and chronic metabolic acidosis) and to begin to educate the family on the basics of the KD. The family’s willingness/ability to adhere to the very rigid requirements of the diet should be ascertained. All medications should be reviewed and changed to the lowest carbohydrate formulations to minimize their potential source of carbohydrates. Laboratory studies should be obtained to determine baseline nutrition status and to rule out disorders of fatty acid metabolism (Table 1).

If the neurologist and the dietitian determine that the patient (and family) is a good candidate for the KD, a hospital admission is scheduled to initiate the KD. According to two recent studies, it is no longer considered necessary to fast a child prior to initiation of the diet, however, without the fasting period prior to starting the diet, it may take one to two days longer to reach full ketosis. Even without fasting, hypoglycemia, acidosis, nausea,

<table>
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<th>Table 1. Baseline Laboratory Recommendations Prior to Initiation of the KD</th>
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<td><strong>Chemistry panel:</strong> electrolytes, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, liver function tests, lipid panel, acylcarnitine panel, carnitine level, urine organic acids, urine metabolic screen, plasma amino acids, uric acid, lactate, and pyruvate</td>
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within normal limits, and have tolerated the patient is discharged once they have tolerated monitoring for adverse effects of the diet. fluid goals, sick day management, and vitamin and mineral supplementation, weigh all food and/or formula ingredients, food preparation, use of the gram scale to intake. See Table 2 for a sample ketogenic ratio of grams of fat to grams of protein. The most common ratio is four grams of fat to one gram of protein plus carbohydrate. The most common ratio is four grams of fat to one gram of protein plus carbohydrate (described as 4:1). At this ratio, 90% of the calories come from fat and 10% from protein and carbohydrate combined. Sometimes it is necessary to provide a lower ratio (such as 3:1) to increase protein or carbohydrate intake. See Table 2 for a sample ketogenic diet at a 4:1 ratio.

During the initiation, the family and other caregivers are thoroughly trained in food preparation, use of the gram scale to weigh all food and/or formula ingredients, vitamin and mineral supplementation, fluid goals, sick day management, and monitoring for adverse effects of the diet. The patient is discharged once they have reached moderate to high ketosis, labs are within normal limits, and have tolerated three ketogenic meals or feedings at the target ratio. The patient is discharged with carbohydrate-free medication prescriptions and follow-up appointments are arranged.

**ADVERSE EFFECTS**

Although there have been numerous research studies of the KD, adverse effects have not been consistently reported in these trials. However, side effects of the KD do occur. The most common short-term side effects of the KD are constipation, acidosis, excessive ketosis, hypoglycemia, and dehydration. Possible long-term effects of the diet that have been reported include growth retardation, gastrointestinal symptoms, carnosine deficiency, and elevated lipids. Other, rare but serious, adverse effects include cardiac abnormalities due to selenium deficiency, Fanconi renal tubular acidosis and kidney stones. Lipid levels, including cholesterol, were noted to increase slightly, but not to a clinically significant degree, and over a two year period, while still on the diet, these elevated levels improved. Long-term studies of children who have been on the KD more than six years found that they are at risk for bone fractures, growth disturbances, and kidney stones. A study of patients who had discontinued the diet after six years found that the majority continued to have greater than 50% reduction in seizures; previously mildly elevated lipids had normalized, and growth was normal as well.

An analysis of the KD (at a 4:1) found that despite the inclusion of nutritious foods, the diet was inadequate for 19 of 23 micronutrients. It is essential that all patients on the KD receive appropriate vitamin and mineral supplementation to meet the dietary reference intake (DRI).

**SUMMARY**

The ketogenic diet remains one of the most effective treatments for medically refractory childhood epilepsy. In spite of the long history of its use, relatively little is known about the mechanism of action. The diet’s efficacy in a wide range of epilepsy syndromes suggests that it may have multiple mechanisms of action, each of which may be more relevant to a specific disease state. Further research is necessary to define the mechanism of action, which may, in turn, lead to easier means to provide the therapeutic benefit.

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**Table 2. Sample Ketogenic Menu at 4:1 Ratio, 1400 calories**

| Breakfast – Scrambled eggs, bacon, and fruit with whipped cream | 38 grams 40% cream (whipped) 25 grams fresh strawberries 17 grams scrambled eggs 13 grams bacon 28 grams butter |
| Lunch – Tuna salad roll-up and baby carrots | 29 grams fresh baby carrots 24 grams tuna fish 28 grams mayonnaise 25 grams iceberg lettuce |
| Dinner – Hamburger patty with Jell-O, fruit, and whipped cream | 25 grams beef 70% lean 27 grams soybean oil 39 grams 40% cream (whipped) 22 grams watermelon 86 grams Jell-O (sugar-free) |

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The Role of New Genetic Technology in Investigating Autism and Developmental Delay

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**INTRODUCTION**

Children with developmental delay and dysmorphic features can present diagnostic and therapeutic challenges. One of the newer genetic technologies, known as chromosomal microarray, or array comparative genomic hybridization (aCGH) has revolutionized our diagnostic capabilities. We describe a patient who had global developmental delay and autistic features who did not receive a diagnosis until aCGH was obtained. Our case illustrates the way that current genetic testing may provide new information for a subset of patients with undiagnosed global delay, intellectual disability (previously termed mental retardation), and autism. To this end, we provide a brief background on the development and utilization of aCGH.

Next, we discuss his particular diagnosis of 22q11 deletion syndrome as an example of the way that knowledge of a microdeletion syndrome may influence current medical management and future approaches. While 22q11 deletion syndrome is a well-known microdeletion, many syndromes of similar consequence await further elucidation and case collection. We conclude by providing resources for physicians and families that may improve knowledge and support for those diagnosed with common and rare genetic syndromes.

**CASE REPORT**

A boy born to a 38 year-old G3 mother and 41 year-old father after a full-term uncomplicated pregnancy with a birth-weight of seven pounds and nine ounces appeared normal at birth, however, the parents became concerned about his development at around eighteen months. He spoke his first words after age two, and spoke in short phrases at age four. He began to walk independently at nineteen months. He was seen at the Children’s Neurodevelopment Center (CNDC) at 20 months. Audiology examination did not reveal significant hearing loss, and the family was provided information on early intervention services. On follow-up visits at the CNDC, it was noted that he had echolalic language, a high activity level, and poor attention span. His preschool teacher reported concerns about his lack of developmental progress, fleeting eye contact, and lack of awareness of his body in space. A formal psychological assessment at age four years, seven months indicated cognitive and adaptive skills at a 22 month level. Speech and language evaluation at four years, nine months found expressive and receptive language skills at a two year level. Behavioral observations revealed decreased social reciprocity and eye contact, limited functional communication and repetitive behaviors. On the Childhood Autism Rating Scale, the patient scored in the mildly-moderately autistic range. He was referred to Genetics Clinic.

Past medical history was significant for three febrile seizures. He had a history of several ear infections and a pilonidal cyst, for which no treatment was necessary. An MRI of his spine and head was normal. Review of systems was positive for episodes when he sometimes appeared to choke on his food.

Figure 1. High density array CGH analysis of patient sample showing a single copy 3 Mb deletion of chromosome 22 including the TBX1, COMT, PROH, and DGCR8 genes. The arrow points to where there is more reference than patient DNA, indicating a deletion of patient DNA.
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Family history did not reveal any major learning problems in either of his parents. His father graduated from high-school and took college courses. Currently, he was taking care of his son full-time. His mother worked as an accountant. She had two sons from a previous relationship, one of whom required some help in school for motor problems. There were no other family members on either side with learning difficulties or birth defects.

On physical examination, he had mildly dysmorphic features including a slightly prominent nose and slight asymmetry of his mouth when crying, but otherwise he resembled his father. He had a faint strawberry hemangioma on his right arm. Neurological examination revealed hypotonia and awkward gait. He had hypernasal speech. The rest of the examination was normal.

A definitive diagnosis could not be made based on history and physical examination, and aCGH was ordered, which revealed a 22q11 deletion (Figure 1); current standards recommend confirmation of aCGH with fluorescent in situ hybridization probe (FISH) (Figure 2). The parents were tested by FISH and did not have the 22q11 deletion (Figure 3).

As per the management guidelines for 22q11 deletion syndrome, he was screened for hypocalcemia and immune deficiency; had a renal sonogram and was referred to a cardiologist. Chest X-ray suggested a right aortic arch, which echocardiogram confirmed. The patient had no evidence of dysphagia or cough with liquids or solid oral intake, so he did not require intervention. He was also referred to Craniofacial Clinic where evaluation documented a palatal zona pellucida and his speech was confirmed as hypernasal. His uvula appeared intact, but his posterior nasal spine could not be adequately examined after he bit the plastic surgeon’s examining finger. Nevertheless, the tentative diagnosis of palatal submucous cleft was made, which may explain his hypernasal speech. He continues to be followed by a multidisciplinary team.

**Discussion**

In recent years, aCGH has at least doubled our diagnostic ability in the work-up of patients with global developmental delays or intellectual disabilities. Recently, the International Standard
Cytogenomic Array (ISCA) Consortium concluded that chromosomal microarray analysis is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies and offers a much higher diagnostic yield (15%-20%) for genetic testing of individuals with unexplained developmental delay than a G-banded karyotype (approximately 3%, excluding Down syndrome and other recognizable chromosomal syndromes). Thus, aCGH has revolutionized clinical cytogenetics, as it provides a relatively quick method to scan the genome for recognizable chromosomal syndromes.2

Therefore, aCGH has revolutionized clinical cytogenetics, as it provides a relatively quick method to scan the genome for gains and losses of chromosomal material with significantly higher resolution and far greater clinical yield than was previously possible with karyotype and other techniques.3

Five years ago, before aCGH became a first-tier test in clinical genetics, the work-up for patients who had dysmorphic features and/or unexplained global developmental delay or intellectual disability began with karyotype, a representation of the chromosomes, which had a five percent diagnostic yield, and in many cases, Fragile X testing, with a yield around 1%.4 The limit of a conventional karyotype is its ability to detect small gains or losses. Typically, for an abnormality to be seen on karyotype, a deletion or duplication would have to span at least 5-10 Mb (of the 3000 Mb human genome).

In the mid 1980s, a new advance allowed for smaller deletions or duplications to be detected than could be seen on routine karyotype, which is known as Fluorescent in Situ Hybridization (FISH). This technique uses fluorescent probes that bind to regions of interest, typically those spanning around 1-4 megabases of genetic material. Probes for several common syndromes, such as Williams, Wolf-Hirschhorn, Smith-Magenis, and 22q11 deletion syndrome (previously called velocardiofacial syndrome or DiGeorge Syndrome) became available. These syndromes can often be diagnosed clinically by facial and other features, and FISH testing can be sent for confirmation. However, patients with mild or atypical cases have often been missed by this approach.

To understand why aCGH offers a more comprehensive test than FISH, it is useful to review the technology behind the technique. In aCGH, slides are arrayed with small segments of DNA as the targets for analysis. DNA is extracted from a test sample (e.g., blood, skin, fetal cells). The test DNA is then labeled with a fluorescent dye of a specific color, while DNA from a normal control sample is labeled with a dye of a different color. With the original technique, the two genomic DNAs, test and reference, are mixed together and applied to a chip. In updated versions, the chip contains the reference DNA to which the patient DNA is applied. Because the DNAs have been denatured, they are single strands that attempt to hybridize with the arrayed single-strand probes. Next, digital imaging systems are used to capture and quantify the relative fluorescence intensities of the labeled DNA probes that have hybridized to each target. The fluorescence ratio of the test and reference hybridization signals is determined at different positions along the genome. The result demonstrates the relative copy number of sequences in the test genome as compared to the normal genome. For example, the control DNA could be labeled red and the patient DNA green. If the spots that represent 22q11 appear to have a higher red intensity, then that means that patient DNA is missing.

The first commercially available arrays used targeted bacterial artificial chromosomes (BACs) that contained DNA isolated from large insert clones that range in size from 150 – 200 kb and only included areas of the human genome that contain known microdeletion or duplication syndromes. The production of BAC DNA was labor-intensive, and resolution remained limited to 50 – 100 kb. Newer arrays, known as oligonucleotide arrays, use artificially synthesized vectors that represent each area of the genome. They are considered preferable to BACs, because they have extremely high resolution, up to 1 kb of the human genome. Since oligoarrays are considered more comprehensive, BAC arrays are already considered obsolete but are still used by some laboratories for confirmation of aCGH results.

In most cases, the microdeletion is considered causative for the patient’s problem based on two major criteria: first, many genes are missing or added in the region and some may be associated with neurodevelopmental or other problems, and second, the same deletion or duplication has been reported in similarly affected individuals.

In some cases, copy number variants are found with DNA missing or added that are also present in the general population, and therefore they are not considered causative. As more testing is performed, better delineation of copy number variants versus pathogenic changes awaits. While a lengthy explanation is beyond the scope of the paper, we refer the reader to a reference that addresses the issue.5

Results can also return with findings called variants of unknown significance (VUS)—changes found on aCGH that have not been routinely found in the general population but are not definitively associated with medical problems. In these cases, parental testing may be helpful. If one parent has the same VUS, it is assumed that it is less likely to be diagnostic (unless the parent has the same condition as the child). If neither parent has the same VUS, the de novo occurrence in the child increases suspicion of a causative role. However, a definitive diagnosis cannot be given, until more cases and information become available.

Challenges of aCGH include: cost and insurance approval for testing, variability in laboratory interpretation, and difficulty in providing adequate genetic counseling for complex test results. Many microdeletions/duplications discovered on aCGH have rarely been described, thus the impact on the child’s prognosis or even care may be uncertain. Families often respond with bewilderment when told of a diagnosis such as “a 15.24.1 three megabase microdeletion” or “15q11 four megabase duplication.” With education, most parents end up successfully understanding and navigating information currently available.

Despite the fact that aCGH is not a perfect test, this state-of-the-art technology has considerable diagnostic power and has become the gold standard for patients who require genetic evaluation. The American College of Medical Genetics currently recommends the use of aCGH for patients with undiagnosed intellectual disability, global developmental delay, multiple congenital anomalies, and autism.6 Recently, the ways in which aCGH
We have found that even well-characterized genetic syndromes have a wide range of expressivity, thus we have cast our net wider in considering which children may have syndromes.

Many patients with microdeletions or microduplications have additional problems beyond the neurocognitive. Thus, by making a diagnosis, we can screen children for medical problems that could otherwise go undiagnosed and make appropriate specialty referral. For example, in individuals with 22q11 deletion syndrome, congenital heart disease, palatal abnormalities, and learning disabilities are present in the majority. Almost 75% have congenital heart disease, particularly cono-trunical malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus). Due to complex cardiac anatomy in some patients, who may even have aberrant subclavian arteries, surgery and intubation can pose a risk, so knowledge of the diagnosis may be life-saving. About 70% of 22q11 deletion syndrome patients have palatal abnormalities, particularly velopharyngeal incompetence (VPI), submucosal cleft palate, and cleft palate. In some patients, VPI may have been missed prior to their diagnosis of 22q11 deletion syndrome. Once diagnosed, associated articulation difficulties and hypernasality may improve with intensive speech therapy but if refractory may require surgical intervention. In addition, over half of individuals have an immune deficiency; about 50% have hypocalcemia, approximately 30% have renal problems, and approximately 30% have conductive or sensorineural hearing loss. Other medical problems in some patients include laryngotracheoesophageal anomalies, growth hormone deficiency, seizures (without hypocalcemia), and skeletal abnormalities.

Interestingly, subsequent evaluations in our case did not reveal any major medical anomalies. An extremely variable phenotype has been repeatedly described when following large cohorts. Like our patient, some individuals with 22q11 deletion syndrome have no systemic manifestations, and other individuals may have few obvious features. For example, researchers tested thirty relatives of affected individuals without any typical manifestations of 22q11 deletion syndrome who were found, by screening, to have a deletion on 22q11. Nineteen were adults ascertained only following the diagnosis in their child, 10 were children identified following the diagnosis in their sibling, and one was a child diagnosed prenatally following the diagnosis in her parent. Sixty percent of patients had no visceral anomalies. Similarly, the range of presentation in all microdeletion syndromes is variable. The second point is that parental testing is considered optimal both for medical management of a potentially affected parent and for prenatal counseling for future pregnancies. In our case, as previously mentioned, the parent’s tests were normal, and we counseled them that their recurrence risk was low.

The most concerning findings in our patient included behavioral difficulties and autistic features. Interestingly, a subset of patients with 22q11 deletion syndrome present with autistic spectrum disorder as a feature. One current area of particular interest has been the effect of 22q11 deletion syndrome on neuropsychology. The psychiatric disorders most commonly reported in children and adolescents with 22q11 deletion syndrome have been attention-deficit/hyperactivity disorder, oppositional defiant disorder, anxiety disorders, and major depression. Psychotic symptoms have been observed in 14% to 28% of children with 22qDS. A 5-year follow-up study of 22qDS children with psychotic symptoms at baseline found they had an increased risk for a subsequent psychotic disorder. In particular, an increased rate of schizophrenia is widely recognized. By knowing that patients with 22q11 deletion syndrome are at risk for psychiatric disorders, physicians can recognize signs and symptoms earlier and provide treatment more promptly.
Genetic studies may affect future medication management of children or adults with 22q11 deletion syndrome and psychiatric problems. The genes catechol-O-methyl-transferase (COMT) and proline dehydrogenase both reside within the commonly deleted region of 22q11.2. It has been hypothesized that in patients with the COMT gene missing as part of their deletion, the COMT insufficiency leads to elevated serum proline levels and abnormal brain function. By studying over fifty children with 22q11 deletions and comparing to healthy controls, researchers confirmed a significant interaction between a COMT deficient genotype, increased proline, and behavioral problems or psychiatric features. The conclusion was that in some patients with 22q11 deletion syndrome, elevated proline negatively affects brain function by an increase in dopamine in the prefrontal cortex (elevated dopamine is more likely due to the reduction of COMT, which metabolizes dopamine, which should be true wherever dopamine is secreted). In the future, one can envision using medications that reduce proline levels in patients with 22q11 deletion syndrome and psychiatric disorders. The future may hold more promising pharmacological interventions targeted for this particular genetic syndrome. The hope for other microdeletion or duplication syndromes is that, like in the case of 22q11 deletion syndrome, genes involved in particular pathology will be further characterized and targeted for pharmacogenetic interventions.

**RESOURCES FOR FAMILIES WITH MICRODELETION OR DUPLICATION SYNDROMES**

When families are faced with a new diagnosis, it is naturally overwhelming but, in some ways, a relief to end their diagnostic odyssey. Genetic counseling helps families learn more about the diagnosis and, in turn, empowers them to advocate for their child’s medical needs. Support groups are especially helpful for families and patients who have rare microdeletion or duplication syndrome diagnoses. These groups invite all families with new diagnoses to contribute information about their child’s medical problems and outcomes and encourage families to connect to those with the same or similar diagnoses via e-mail, phone, and even in person.15

**CONCLUSION**

In recent years, with the widespread use of aCGH in the work-up of patients with global developmental delay, the diagnostic yield of genetic testing has increased considerably. We have found that even well-characterized genetic syndromes have a wide range of expressivity, thus we have cast our net wider in considering which children may have syndromes. Patients may receive commonly reported diagnoses such as 22q11 deletion syndrome or diagnoses of more rare microdeletion or duplication syndromes. For all these patients and families, we are optimistic that the future holds more genotype-phenotype correlations, understanding of particular medical problems, and even pharmacogenetic interventions.

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Mrs. K is a 67-year-old woman presenting for a brief follow-up visit. You treated her for an E. coli urinary tract infection last month, but she feels well today and offers no complaints. Her blood pressure and lipids are well controlled on low doses of a single antihypertensive and a lipid lowering agent. She still struggles with smoking, but has cut down to a few cigarettes a day. She also reports her husband has finally turned over the family business to their children, and they are enjoying spending more time together. When you ask if there is anything else she needs, she hesitates for a moment before asking, “Is there anything I can do to make sex more comfortable?”

On further questioning, Mrs. K states she and her husband have become more intimate since his retirement, but that attempts at intercourse have been painful and caused bleeding. At times her vagina is dry and burns, but at other times there is a thin yellow discharge. An over-the-counter douche made the burning worse. A friend suggested an herbal supplement which she tried for a few weeks without success. She used to enjoy sex but is concerned that part of her life “is over for good.” You suspect her complaints are related to vulvovaginal atrophy.

Vulvovaginal atrophy, also known as atrophic vaginitis, results from the decline in endogenous estrogen secretion after menopause, which induces thinning of the vulvovaginal epithelium with associated inflammatory changes. It is common in older women but not always symptomatic. Unlike vasomotor symptoms, which occur early in menopause and usually resolve, vulvovaginal atrophy presents later and is persistent and progressive. True incidence and prevalence are unknown. Estimates suggest up to half of postmenopausal women are symptomatic, but a quarter of these will not seek treatment.

Estrogen is essential to maintaining the urogenital environment. After menopause, the vaginal epithelium thins while subepithelial connective tissue increases, resulting in loss of rugal folds and elasticity. Vaginal epithelium is a rich source of glycogen, which in turn supports lactic-acid producing bacteria. The loss of lactobacilli and subsequent increase in vaginal pH that accompany estrogen deficiency allows overgrowth of gram negative rods, which may predispose to urinary tract infection. Finally, blood flow is reduced, producing a decline in vaginal secretions.

All postmenopausal women are at risk for vaginal atrophy. Smokers are more estrogen deficient compared with nonsmokers and may be at higher risk. Engaging in regular sexual activity, whether through intercourse or masturbation, appears to decrease risk, possibly through increased blood flow. Women using anti-estrogen medications, such as aromatase inhibitors for adjuvant treatment of breast cancer, are more likely to experience severe symptoms.

Women may not volunteer symptoms related to vulvovaginal atrophy. The symptomatic woman can experience vaginal dryness, burning, and pruritus; yellow, malodorous discharge; urinary frequency and urgency; and pain during intercourse and bloody spotting afterward. With advanced atrophy, penetration during intercourse may be impossible. Recurrent urinary tract infections may occur.

Typical findings on external genital exam include sparse pubic hair, decreased turgor and elasticity of the vulva, fusion of the labia minora, and eversion of the urethral mucosa. The vaginal exam should be approached carefully, with evaluation of the width and depth of the introitus before attempting to insert a speculum. A narrow Pederson speculum is a better choice than the broader Graves speculum. The vaginal exam shows pale, smooth, shiny mucosa that may be friable and bleed with minimal trauma. The vagina may be dry or there may be watery to serosanguinous discharge. Fissures, diffuse or patchy erythema, petechiae, or visible vessels are common findings. Cystocele, rectocele, or uterine prolapse may also be present.

Vulvovaginal atrophy is primarily a clinical diagnosis in older women, but select testing can help rule out coexisting conditions suggested by specific symptoms:

- Urinary urgency or frequency: urinalysis and culture to rule out urinary tract infection
- Vaginal discharge: microscopy of saline and potassium hydroxide wet preps to evaluate for bacterial vaginosis and vaginal candidiasis
- Postcoital spotting: cervical cultures or urine testing for gonorrhea and chlamydia
- Vaginal bleeding: transvaginal ultrasound to evaluate for endometrial overgrowth
- Labial or vaginal wall lesions: biopsy to evaluate for dermatologic conditions such as lichen planus or malignancy
Whether treatment is needed in asymptomatic women is unknown. Lifestyle modification and over-the-counter vaginal moisturizers and lubricants should be considered as first-line treatment. Women should be counseled to avoid tight-fitting clothing, synthetic undergarments, and contact irritants such as scented soaps and feminine hygiene products. Regular use of vaginal moisturizers (such as Replens) can help relieve vaginal itching and irritation, while water- or silicone-based personal lubricants (such as Astroglide or Eros) during intercourse can reduce dyspareunia.

Estrogen-based treatment restores vaginal epithelium, pH, and moisture, and should be considered when non-hormonal treatments fail. Although there are few well-designed trials, topical therapy is preferred for isolated vaginal symptoms given concern for long-term risks of malignancy and cardiovascular disease with systemic hormone replacement therapy (HRT).

Local estrogen treatment may also be helpful in women taking ultra-low-dose HRT for vasomotor symptoms. If urogenital symptoms are not relieved, the addition of topical estrogen may limit total estrogen dose compared with use of higher dose HRT.

Topical estrogen is available in several forms (see table). There are insufficient data to recommend any single treatment as superior, so patient preference should guide selection. Vaginal symptoms typically respond within a few weeks. Side effects may include breast and perineal pain, local irritation, and endometrial proliferation.

Estrogen exposure is assumed to be minimized with topical therapy, but systemic absorption does occur. Creams have the highest association with systemic absorption, followed by tablets then rings. Safety beyond one year is unknown. Use of the lowest effective dose for the shortest duration possible is recommended.

Although endometrial protection is not routinely recommended, addition of a cyclic or daily progestin to prevent endometrial hyperplasia should be considered with long-term or higher dose (>0.5 mg estradiol or >0.5 g conjugated estrogens/day) topical therapy.

Estrogen is contraindicated in known or suspected breast or other estrogen-dependent cancers, undiagnosed vaginal bleeding, history of thromboembolism, or active thrombophlebitis. Use in a woman with breast cancer with severe urogenital atrophy unresponsive to non-hormonal treatment should be considered only after careful discussion of risks with the woman and her oncologist. There is additional concern for women using adjuvant therapy for breast cancer as there may be sufficient systemic absorption from topical estrogen to counteract the anti-estrogenic effects of aromatase inhibitors.

Estrogen use should be reviewed every 3 to 6 months, with an attempt to taper or discontinue its use. Discontinuation often results in symptom recurrence. Women using estrogen should have an annual clinical breast exam and mammography. Vaginal bleeding should prompt transvaginal ultrasound to evaluate for endometrial overgrowth, with endometrial biopsy as indicated.

<table>
<thead>
<tr>
<th>Dosing form</th>
<th>Strength</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogens vaginal cream (Premarin)</td>
<td>0.625 mg/gram</td>
<td>0.5-2 grams vaginally daily for 3 weeks, then tapered to lowest</td>
<td>• Less acceptable to women than vaginal tablet or ring, which may affect adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>effective dose twice weekly; administer cyclically (3 weeks on, 1 week off)</td>
<td>• Highest association with systemic absorption</td>
</tr>
<tr>
<td>Estradiol vaginal cream (Estrace)</td>
<td>0.01 mg/gram</td>
<td>2-4 grams vaginally daily for 1-2 weeks, then tapered to lowest</td>
<td>• Difficult to accurately measure lower doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>effective dose over 1-2 weeks; administer 1-3 times weekly for</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>maintenance</td>
<td></td>
</tr>
<tr>
<td>Estradiol tablet (Estrace)</td>
<td>0.01 mg</td>
<td>1 tablet vaginally daily for 2 weeks, then twice weekly for</td>
<td>• Less systemic absorption compared with cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>maintenance</td>
<td></td>
</tr>
<tr>
<td>Estradiol-impregnated silicone vaginal ring (Estring)</td>
<td>2 mg</td>
<td>Ring placed vaginally every 3 months (delivers approximately 0.0075 mg/day)</td>
<td>• May be inserted by patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lowest association with systemic absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May not be appropriate for women with narrow, short, or stenosed vagina</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Expulsion more common in women with prior hysterectomy</td>
</tr>
</tbody>
</table>

Table 1. Topical estrogen therapy for vaginal atrophy
The need for surveillance ultrasound in asymptomatic women is unknown.

There has been considerable interest in bioidentical hormones as well as complementary medications, including phytoestrogens, black cohosh, dong quai, ginseng, and red clover, but data on their effectiveness are limited.

Vulvoaginal atrophy is a common, but often unrecognized, condition in older women that can significantly affect daily life. Clinicians who care for older women should be alert to possible clues and specifically inquire about symptoms. Effective interventions are available, although more study is needed regarding the long-term safety of topical estrogens. Given concerns for systemic effects of topical estrogens, there is significant research interest in more targeted therapies, such as vaginally delivered selective estrogen response modifiers.

For Mrs. K, her symptoms provided the motivation to quit smoking. Lifestyle modification and a topical moisturizer were not completely effective, but she experienced significant improvement after treatment with the estradiol vaginal tablet.

**RESOURCES**


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Less Than Optimal Oral Health Care During Pregnancy in Rhode Island Women: Oral Health Care as a Part of Prenatal Care

Junhie Oh, BDS, MPH, Laurie Leonard, MS, Deborah Fuller, DMD, MS, and Katherine Miller, BA

It is well-documented that hormonal and immunologic changes during pregnancy predispose women to various oral health problems including gingival/periodontal swelling or inflammation, tooth erosion, and dental decay.1,2,3 The receipt of preventive and therapeutic oral health services can prevent further complications of dental diseases during pregnancy and the postpartum period. Furthermore, current evidence-based research demonstrates the potential benefits of maintaining good oral health during pregnancy to control other common pregnancy complications, such as gestational diabetes and preeclampsia (pregnancy-induced hypertension). Studies have suggested that gingival or periodontal infection-related bacteria can adversely affect the glycemic control of gestational diabetes and the pathogenesis of preeclampsia.4,5,6 In addition, evidence shows that cariogenic bacteria are typically transmitted from mother to her child.7,8 Pregnant women and potential caregivers who have extensive past or current tooth decay should be advised during pregnancy about the use of fluoride, antimicrobial products such as xylitol and chlorhexidine, dietary control, and behavioral changes and techniques to reduce cariogenic bacteria transmission to their babies.9

The Rhode Island Oral Health Program promotes a dental visit for all pregnant women to obtain counseling on oral health care and dental hygiene, preventive services, and treatment needed during their prenatal care period. However, no report has yet been available to assess oral health care access and utilization status of Rhode Island’s pregnant women. The objectives of this report are to (a) document the most recent estimates of Rhode Island women who received dental care during their pregnancy, (b) determine the prevalence of oral health care education provision for women in their prenatal care period, and (c) discuss how Rhode Island can ensure that all women obtain appropriate oral health care and education during their prenatal period.

METHODS

The data used for this analysis were obtained from the 2009 Rhode Island Pregnancy Risk Assessment Monitoring System (PRAMS). PRAMS is an ongoing statewide mail-survery with a telephone follow up component. Women who recently gave birth are randomly selected from the Vital Records birth file. PRAMS collects self-reported information on maternal and infant health behaviors and experiences that occur before, during, and after pregnancy. The survey is supported by the Centers for Disease Control and Prevention (CDC), and 37 states currently participate in PRAMS. Rhode Island began conducting PRAMS in 2002 and has achieved a weighted response of at least 70% each year since. The Rhode Island PRAMS Program sent questionnaires to 1,853 women who delivered a live birth in 2009 and received responses from 1,294 women (71.4% weighted response rate).

Table 1. Percent of Rhode Island Women Who Went to a Dentist or Dental Clinic During Pregnancy, 2009 Rhode Island PRAMS

<table>
<thead>
<tr>
<th>Variable Category</th>
<th>Sample size*</th>
<th>Weighted % (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>1,243</td>
<td>52.7 (49.3–56.1)</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>113</td>
<td>37.3 (25.9–48.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>20–29</td>
<td>595</td>
<td>45.4 (40.5–50.4)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>535</td>
<td>65.0 (60.1–70.0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>697</td>
<td>60.8 (56.4–65.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other</td>
<td>546</td>
<td>41.8 (36.5–47.1)</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤High school</td>
<td>494</td>
<td>44.1 (50.2–61.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>College or higher</td>
<td>647</td>
<td>60.4 (35.2–44.1)</td>
<td></td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$25,000</td>
<td>457</td>
<td>42.4 (36.7–48.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>$25,000–$49,999</td>
<td>235</td>
<td>40.4 (32.6–48.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;$50,000</td>
<td>466</td>
<td>70.9 (65.9–75.9)</td>
<td></td>
</tr>
<tr>
<td>Residential area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core city (6 towns)</td>
<td>665</td>
<td>44.6 (39.9–49.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Rest of Rhode Island</td>
<td>578</td>
<td>60.3 (55.3–65.2)</td>
<td></td>
</tr>
<tr>
<td>Prenatal coverage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid/Rite Care</td>
<td>598</td>
<td>40.5 (35.5–45.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other</td>
<td>645</td>
<td>63.9 (59.3–68.4)</td>
<td></td>
</tr>
<tr>
<td>WIC participation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>617</td>
<td>42.1 (37.2–47.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No</td>
<td>626</td>
<td>62.6 (58.0–67.3)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>0.3073</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>682</td>
<td>54.5 (50.0–59.0)</td>
<td></td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>208</td>
<td>49.0 (40.2–57.8)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>321</td>
<td>48.9 (42.0–55.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Unweighted sample sizes for each category may not add up to 1,243 because of missing and excluded data (responses of “don’t know,” “not sure,” or refused).

† CI = confidence interval

1 Central Falls, Newport, Pawtucket, Providence, West Warwick, and Woonsocket as defined by the population statistics of more than 15% of the children living in families below the federal poverty income level.
The outcome variables in this report are (a) women’s dental visit during pregnancy, and (b) discussion of dental care by a health care worker during pregnancy. The proportional data were weighted to the probability of selection, non-response and non-coverage, and adjusted to reflect the sample stratification on the state birth certificate file. In addition, bivariate analyses using the chi-square test were done to identify any significant differences between the various groups, with respect to women’s dental visit during pregnancy. The statistical significance was tested at P<0.05. SAS survey procedures were used for the analyses in the study to account for the complex sampling design.

**Results**

Overall, approximately half of Rhode Island women reported they had a dental visit during their pregnancy (52.7%, 95% CI=49.3%–56.1%, Table 1). The proportion of pregnant women who visited a dentist or dental clinic was not uniform by age, marital status, educational attainment, household income level, or residential area. Women who were younger than 30 years of age, those who were not married, those who had lower education attainment or lower household income level, or women who lived in urban core cities were less likely to have a dental visit (Table 1). Only 40.5% of women who had prenatal care coverage by Medicaid/RIte Care and 42.1% of women who participated in WIC (Special Supplemental Nutrition Program for Women, Infants, and Children) were seen by a dentist or other oral health professional during their pregnancy (Table 1).

Many Rhode Island pregnant women did not receive oral health counseling from health care professionals during their prenatal care period. As shown in Figure 1, approximately half of women were advised on how to care for their teeth or gums (52.2%). Oral health care was not as frequently discussed with mothers as other prenatal health issues such as safe medicine uses (90.2%), breastfeeding (85.6%), HIV testing (81.9%), maternal depression (73.2%), alcohol consumption (72.7%), and smoking (70.5%).

**Discussion**

**Opportunities to Improve Pregnant Women’s Oral Health Care Access**

According to the 2009 PRAMS findings, many Rhode Island women did not seek dental care during their pregnancy. There could be several reasons behind this finding. Similar to population-based surveys conducted in other states,10 many Rhode Island women may not be aware of the importance of maintaining good oral hygiene and controlling oral disease during pregnancy.

In addition, less than optimal prevalence among Rhode Island women for visiting the dentist during pregnancy may be attributed to a lack of oral health care information and counseling in the prenatal health care setting. As found in this report and other studies, prenatal professionals (obstetricians, family physicians, and other prenatal care providers) do not routinely introduce oral health care topics, screen women’s oral health care needs during prenatal care, or refer their patients to a dentist or dental clinic for examinations, preventive services, or required treatment.11 Oral health education should be included as an integral part of prenatal care, and patients should be informed about the importance of maintaining good oral health during pregnancy and the relationship between maternal oral health status and future caries risk of their child.

Oral health professionals must address unnecessary treatment delay or deferral. Dentists often postpone treatment for pregnant women because they may not fully understand the physiological changes that occur during pregnancy and fetal development, or have misconceptions about the effect of dental treatments on pregnant women and their fetuses.12 However, most dental problems can be treated with no alteration or modification of routine dental procedures. Further, the benefits of providing oral health care during pregnancy far outweigh potential risks when compared to the risk of not providing care. Evidence-based practice guidelines are currently available for dental and prenatal care providers.12,13,14

The prenatal period is an opportune time for women to access oral health services, particularly for low-income women who receive Medicaid/RIte Care dental insurance benefits only during their pregnancy. Financial barriers can be reduced or eliminated for these women by the comprehensive dental care benefit provided by Rhode Island Medicaid/RIte Care. However,
according to 2009 PRAMS data, the dental care benefit was not effectively utilized by Medicaid/Rite Care participants. Additionally, education efforts must be maintained and expanded for pregnant women who may not be aware of the covered dental services or who may face additional barriers, such as finding a dental provider or lack of transportation, to ensure all pregnant women receive preventive oral health services.

**Conclusion**

All pregnant women should obtain oral health services and oral health promotion/disease prevention education. Controlling oral diseases and improving oral health during pregnancy not only enhances women’s overall health but also contributes to improving the oral health of their children. The Rhode Island Oral Health program promotes the integration of oral health into prenatal care. Prenatal care providers can play an important role in raising awareness about the importance of oral health during pregnancy and removing barriers to oral health care. Prenatal care providers are encouraged to identify risk factors for oral disease, make a timely referral to an oral health professional for comprehensive evaluation during pregnancy, and promote completion of all necessary treatment during pregnancy. A coordinated effort between dental and prenatal professionals can benefit maternal and child health outcomes.

**References**


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INTRODUCTION

Pelvic arteriovenous malformations (AVM) are rare and may be congenital or acquired and commonly mimic more common disorders. We describe a young adult male with pulmonary complaints who was found to have acute renal failure, hydronephrosis, congestive heart failure and multiple midline pelvic varices secondary to pelvic AVMs. We report this case to alert physicians to the diverse spectrum and diagnostic difficulties of pelvic AVMs.

CASE DESCRIPTION

A 31 year old male presented with four days of cough and dyspnea. Physical exam: dry mucous membranes, systolic ejection murmur at the right base. Labs: acute renal failure with creatinine 3.17 and BUN 99 (units). CXR: left lower airspace disease. Renal ultrasound (Figure 1): mild bilateral hydronephrosis and numerous midline pelvic varices. Abdominal CT without contrast: bilateral hydronephrosis, no renal calculi, thickened bladder wall. CT confirmed left lower lobe pneumonia. He was treated for community-acquired pneumonia.

Respiratory symptoms improved, renal function normalized after Foley catheter placement. Repeat CT without and with intravenous contrast (Figure 2): varices of the pelvic veins causing low grade obstruction of ureters. The right common iliac artery, internal and common iliac vein and IVC were dilated; cardiomegaly was noted. Angiogram (Figure 3): large complex right pelvic AVM supplied from the right internal iliac artery branches with drainage into enlarged, tortuous bilateral iliac veins and IVC.

Cystogram: extrinsic compression with bladder narrowing. Bladder mucosa was hypervascular with mild ridging of the trigone mucosa. Since he had an elongated prostatic urethra and elevated post-void residuals, he was started on alpha blockade and instructed to double void. Ultrasound 6 months later: resolved hydronephrosis, improved post-void residual.

Cardiology consultation felt cardiomegaly was related to chronic shunting from pelvic AVM and he has been scheduled for endovascular embolization.
Pelvic AVMs in men are rare; less than 20 case reports have been described in the world literature. AV malformations can either be congenital or acquired after surgery or trauma. Many lesions are asymptomatic, discovered incidentally during evaluation for unassociated complaints, as in our patient with pneumonia. Typical manifestations are lower abdominal discomfort, vaginal or rectal bleeding, gross hematuria, urinary frequency or incontinence, impotence in men, lower back pain or rarely heart failure. Uncommonly a pelvic mass may be detected on pelvic or rectal exam; rarely a groin bruit or palpable groin thrill is appreciated. Non specific signs and symptoms mimicking more common disorders may lead to misdiagnosis or delay in diagnosis.

Ultrasonography may reveal anechoic tubular structures with results on color Doppler depending on amount of blood flow. Pelvic CT and MRI can demonstrate extent of disease to plan therapy. Angiography best delineate flow characteristics of lesions, feeding vessels, draining veins, and relationship to normal circulation and can often be therapeutic.

**REFERENCES**


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The authors and/or spouses/significant others have no financial interests to disclose.

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Information for Contributors

Medicine & Health/Rhode Island is peer-reviewed, and listed in the Index Medicus. We welcome submissions in the following categories:

**Contributions**
Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files (jpeg, tif, or pdf).

**Creative Clinician**
Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

**Point of View**
Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

**Advances in Pharmacology**
Authors discuss new treatments. Maximum length: 1200 words.

**Advances in Laboratory Medicine**
Authors discuss a new laboratory technique. Maximum length: 1200 words.

**Images in Medicine**
Authors submit an interesting Image, with a 300-400 word explanation.

For the above articles: Please submit an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, John Teehan, e-mail: jdtuehan@rimed.org. For additional information, phone: (631) 903-3389. Faxes may be sent to (401) 826-1926.

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**Physician’s Lexicon**

The Oracular Words from Delphi

On the southern slopes of Mount Parnassus, in central Greece, stands an ancient shrine dedicated to the spirit of Apollo and the Oracle of Delphi. It was widely believed to represent the center of the earth; and within its sanctuary was the omphalos, a sacred stone representing the navel of the world. The shrine was initially dedicated to Gaia, mother goddess of all mankind; and the Greek word, delphus, signified the womb or uterus of all of humanity. (Uterus, a Latin term, descended from a Greek word, udrios, meaning belly.)

Apollo, in his many voyages, was believed to be carried over the seas by a fish without scales, now called the dolphin (and derived from the Greek, delphus). The oldest sons of the kings of France, and hence the heirs-apparent to the French throne, each inherited a heraldic banner adorned with two dolphins. Their title, in time, came to be “Le Dauphin,” and in more modern times, the Dauphin.

Delphic, as an adjective, has also come to mean anything pertaining to the oracle of Delphi, and in general, any prophetic announcement.

The uterine anomaly characterized by a double cavity is called didelphic meaning two uteruses. And Didelphis defines the genus of marsupials with bilocular uteri, a genus which includes the opposum.

The delphus root has assumed a broader meaning in the non-medical literature. Those nurtured within the same uterus—either simultaneously or sequentially—are said to be brotherly souls. And if those motivated by the non-violent, Quaker philosophy of William Penn (1644 – 1718) wished to form a city of brotherly love, it was inevitable that they would name it, Philadelphia (from the Greek, philos, meaning loving or interested in, as in words such as philosophy, philanthropy, philharmonic, anglophile or philology but not philippics, an invective form of oratory named after the speeches of Demosthenes denouncing Philip of Macedon, or philistine, a word from the Akkadian, palastu. This Semitic root gave rise to the current geopolitical word, Palestine.

The botanical vocabulary is enriched by a number of words derived from the Greek word, delphus, including the delphinium plant commonly called the larkspur; and adelphous, meaning a plant with many stamens. The adjective, adelphous, may also mean brotherly or fraternal. And, accordingly, a university on Long Island bears the name Adelphi.

– Stanley M. Aronson, MD

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**VITAL STATISTICS**

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence
Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>Underlying Cause of Death</th>
<th>Reporting Period</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>May 2010</td>
</tr>
<tr>
<td></td>
<td>Number (a)</td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>197</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>220</td>
</tr>
<tr>
<td>Cerebrovascular Diseases</td>
<td>29</td>
</tr>
<tr>
<td>Injuries (Accidents/Suicide/Homicide)</td>
<td>61</td>
</tr>
<tr>
<td>COPD</td>
<td>47</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,053,209. (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

**VITAL EVENTS**

<table>
<thead>
<tr>
<th>Vital Events</th>
<th>Reporting Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>November 2010</td>
</tr>
<tr>
<td>Live Births</td>
<td>935</td>
</tr>
<tr>
<td>Deaths</td>
<td>857</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Marriages</td>
<td>306</td>
</tr>
<tr>
<td>Divorces</td>
<td>283</td>
</tr>
<tr>
<td>Induced Terminations</td>
<td>289</td>
</tr>
<tr>
<td>Spontaneous Fetal Deaths</td>
<td>95</td>
</tr>
<tr>
<td>Under 20 weeks gestation</td>
<td>89 (89)</td>
</tr>
<tr>
<td>20+ weeks gestation</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

* Rates per 1,000 estimated population
# Rates per 1,000 live births

Note: Totals represent vital events that occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
**Ninety Years Ago, May 1921**

Dr. Robert B. Greenough discusses the value of radium in the treatment of disease, and notes that despite ten years of availability in the US, there exists still an uncertainty among surgeons and physicians as to its value in the treatment of disease. While at one point the general public greeting radium as a "magical element" its actual use has yielded disappointing results, but at the same time medical professionals have gained greater knowledge of its uses and advantages. While pointing out the sacity of radium, Dr. Greenough continues by enumerating some of its successful applications in laboratory testing, diagnostic imagery, and the inhibition of cancerous growth.

In response to Dr. Greenough, Dr. Isaac Gerber expresses his own experience with radium instilling "a very, though not altogether pessimistic attitude towards cancer." Dr. Gerber feels that eventually the use of radium will not be in the field of cancer, but in the treatment of various benign lesions.

An editorial notes an increase in the number of specialists, and that the field of specialization has been divided up more and more. As a result, general practitioners may find it more difficult to maintain a place in the community. "If the modern trend toward extreme specialization is allowed to continue, the general practitioner will disappear. This would be a calamity..." the writer goes on to say that both specialists and general practitioners are essential in the present development of civilization, and that a means should be found to preserve the two. The Council of Medical Education proposes a remedy in which medical curriculums vow to develop general practitioners, and that specialties be made part of a post-graduate teaching, and that there be established certain standards for specialists so that when a patient pays an extra fee, they are sure that the fee represents special knowledge that the recipient has gained by extra time spent in perfecting their special subject.

**Fifty Years Ago, May 1961**

This issue opened with a discussion on the nature of the country's social security program and the various distortions and misrepresentations being presented to the American people. The author quotes an article by Ray M. Peterson, vice president and associate actuary of the Equitable Life Assurance Society of the United States appearing in the April 8 issue of JAMA which declares that: 1.) the public is being given the false impression about the financing of the social security program, 2.) the program has been misrepresented as a "time-tested" and "tried and proved" system of financing old-age benefits, and 3.) that people are under the mistaken impression that benefits are being paid out of reserves rather than an almost-entirely pay-as-you-go system. The author points out that under private insurance, all money paid into the insurance fund together with all income from investment is enough to cover all promised or guaranteed benefits. The piece closes with, "Will the youngsters of the future protest what the oldsters of this generation have voted for themselves? During the decade ahead, will we oldsters, as we seek to enjoy our social security benefits, hear a rising clamor of unfairness—a din of inequity?"

Dr. Mark D. Altschule writes about biochemical aspects of psychiatry. In particular, he attempts to relate the clinical effects of some of the recently introduced drugs for mental and emotional disorders to their actions on brain amines and on some of their derivatives.

Banice M. Webber, MD, Leland W. Jones, MD, and Joan Dockery, RN, look at experiences with human tumor vaccines. Noting that for over fifty years, investigators in cancer therapy have been exploring the possible application of immune mechanisms to the treatment of this group of diseases. Attempts to immunize an individual against their own tumor have been based on the hypothesis that a tumor is in some way antigenetically different from the host and that the host resistance can be increased. They conclude that while results have not been dramatic, their experiences warrant further trials, particularly in combination with X-ray therapy.

Within the editorial section, a letter is reprinted from the Pawtucket Times under the heading "Socialism and Medical Care." It begins: "Proponents of the proposal to provide federal medical aid to everyone over 65 receiving benefits under social security deny their program would be an opening wedge to socialized medicine. The Socialist part of the United States apparently thinks otherwise."

In a short note to lexicographers, the identical meanings of "flammable" and "inflammable" are pointed out. The World Health Organization recognizes that language is full of opposites such as formal and informal, decent and indecent, and capable and incapable. With that in mind the WHO recommends flammable with an opposite non-flammable.

**Twenty-Five Years Ago, May 1986**

Dianne N. Abuelo, MD, Judith Rosenstein, BA, MT, and Michael Sheff, PhD bring up the subject of Tay-Sachs disease, a fatal neuro-degenerative disorder transmitted by a pair of autosomal recessive genes. A recent decline in incidence among the Jewish population of the United States is attributed to extensive efforts in community education and heterozygote screening. Premarital rabbinical counseling provides the ideal opportunity to encourage screening.

Under "Have You Heard?", state licensing boards will be alerted by the American Medical Association when physicians have licensure actions taken against them in other states. Elsewhere, it's noted that air guns that fire pellets had usually been considered dangerous only to unprotected eyes, that pellets can also penetrate the abdomen and require surgical removal.
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