

# PEDIATRIC NEWS

## San Antonio Military Pediatric Center



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### Housestaff Puzzler: Stevens-Johnson Syndrome and the Use of Lamotrigine

Jordan Pinsker CPT MC  
PL2  
San Antonio Military Pediatric Center

**A**n 8 year old white male with a history of bipolar disorder, oppositional defiant disorder, and tourette syndrome presented to the BAMC emergency department with a new rash. He reported that the rash started as small red bumps over his groin, but over the last 3 days the rash progressed up his trunk, back, and face. This rash was intermittently pruritic, but not painful. He also had temperature of 100.4 (F) the day prior, but was febrile to 104.3 (F) on the day he presented. He complained of 1 day of URI symptoms including cough and congestion. He reported no sick contacts. The patient's past medical history was significant for bipolar disorder, tourette syndrome, and oppositional defiant disorder. He had been psychiatrically hospitalized twice in past year for suicidal ideations. His family history is significant for depression.

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### STI's (STD's) in the Pediatric Clinic

Dale M. Ahrendt Maj MC  
Chief, Adolescent Medicine  
SAMPC

**S**exually Transmitted Infections can be seen and managed outside of the Adolescent Clinics. Their diagnosis and treatment no longer has to involve the feared "Gyn exam" or urethral swab. Urine testing is now available at WHMC and BAMC for N. Gonorrhea and Chlamydia trachomatis. In this article I will discuss 1) The new urine tests available 2) Tests for other STI's 3) What to do with a positive result 4) Recommended treatment regimens.

The Urine tests now available are actually more sensitive than the cervical or urethral swab that has been done in the past. These tests are so good they are actually better than the "gold standards" used to judge their sensitivity. The tests are done in-house at BAMC and will soon be done in-house at WHMC. The test being done is classified as a nucleic acid amplification test. With these tests, the sample submitted undergoes a process that amplifies nucleic acid sequences that are specific for GC and Chlamydia. This means viable organisms are not required, which makes handling of the samples much easier. Our laboratories are using a test that uses transcription mediated amplification (TMA), although the computer still lists it as an LCR. The turn-around time for the tests can be a bit longer – up to a week or two. In a patient with symptoms it is best to treat presumptively (discussed later) pending the test results. All sexually active males and all sexually active females that have had new partners or exposures since their last Pap smear can and should be screened using these tests. Remember these tests can be done confidentially in adolescents, meaning no parental permission or notification is required. Parental notification without permission is actually not legal. (TX

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### Autistic Spectrum Disorders Part 1

LTC Stephen Greefkens LTC MC  
Developmental Pediatrics  
San Antonio Military Pediatric Center

**A**utism and it's variants have gained significant notice in recent years both in public eye (cover of TIME magazine; May 2002) and among health care providers who are faced with diagnosing, managing, and counseling parents about this puzzling and challenging group of children. With evidence that the prevalence has increased markedly in recent years as well as the knowledge that early, intense, behavioral and educational interventions

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Family Code 32.003&32.004) It is a good idea to ask the patient for a phone number where they can be reached, or arrange for a time when they can follow-up for results.

Testing for other STI's should also be offered. Screening for HIV, Syphilis, and hepatitis should be considered. At WHMC, HIV testing requires a specific consent form be signed and sent with the patient. At BAMC, documentation of informed consent is all that is required. During your pre-testing counseling, it is important to explain to them that this is an anti-body test with a latency time between exposure and seroconversion. If there is concern about a contact within the previous 6 months, it is best to recommend re-testing again after at least 6 months have passed. It is advisable to tell your patients that they need to follow-up in person for their HIV test results. Telling them you can give negatives over the phone, but they have to come to the clinic for positives could have a disastrous outcome when you actually try to get them to return for their results. Post-test counseling should involve reviewing the latency period and recommendations for re-testing, as well as ways to decrease their risk for exposure in the future.

Herpes is a diagnosis often made based on clinical appearance of the lesions. Viral culture and PCR can be unreliable unless fresh vesicles are available for sampling. Testing should still be attempted when appropriate, but should not be used to "rule-out" the diagnosis if the lesions are several days old.

HPV is also a diagnosis often made based on appearance in most patients. The new wet prep pap smear offers the added advantage of identification and viral sub-typing of the HPV virus in females.

If you get a positive test result for GC, Chlamydia, HIV or Syphilis, in addition to treating the patient the results must be reported to the hospital Public Health office. At WHMC you can call them at 292-7253 or fax a reportable diseases form at 292-2524. At BAMC, Public Health can be reached at 916-2768. If you have a special phone number that the patient prefers to maintain confidentiality, you can relay that information to them at that time. You can also send the patient directly after they see you in follow-up. They will interview your patient so that contacts can be identified.

The 2002 MMWR Treatment Guidelines<sup>1</sup> recommend the following treatment regimens for uncomplicated cervicitis or urethritis:

#### Chlamydia

Azithromycin 1 gram orally in a single dose (use four 250mg pills, not the 1 gram slurry for better compliance) OR Doxycycline 100mg orally twice a day for 7 days. Alternative regimens include Levofloxacin 500mg once a day for 7 days.

#### N. gonorrhoea

Multiple single dose regimens including Cefixime 400mg PO, (*No longer available. Ed*) Ceftriaxone 125mg IM, & Levofloxacin 250mg PO are recommended. Resistance to fluoroquinolones has been growing, making it an "inadvisable" choice in Hawaii or the west coast, and in patients that may have acquired the infection in those areas.

Because most of the tests available for Chlamydia had poor sensitivity, treating for both organisms with all positive GC tests was previously recommended. Because of the increased sensitivity, this recommendation has been modified in the 2002 guidelines to treat for

both only if Chlamydia has not been ruled out. Because the urine TMA is better than the gold standard, it's exact sensitivity is hard to accurately quantify. My clinical opinion is that it is best to continue to treat for both unless there is a clear contraindication, such as antibiotic allergies.

For ascending infections, such as suspected epididymitis or pelvic inflammatory disease (PID), one-time treatment regimens are not sufficient. The 2002 guidelines make the following recommendations:

#### Epididymitis

Ceftriaxone 250mg IM in a single dose, PLUS Doxycycline 100mg PO BID for 10 days. Alternatives include Levofloxacin 500mg PO for 10 days. Keep in mind the growing fluoroquinolone resistance when using an alternative regimen.

#### PID

If oral treatment is appropriate\*, Levofloxacin 500mg PO for 14 days, or Ofloxacin 400mg PO BID for 14 days WITH OR WITHOUT Metronidazole 500mg PO BID for 14 days

OR

Ceftriaxone 250mg IM or Cefoxitin 2 grams IM and Probenecid 1 gram PO administered concurrently PLUS Doxycycline 100mg PO BID for 14 days WITH OR WITHOUT Metronidazole

\*PID is likely underdiagnosed according to many reports. One episode of PID can result in a risk of infertility as high as 21%, and as high as 75% with 3 or more episodes. If you have sufficient data to strongly consider the diagnosis, it is best to begin treatment without waiting for test results. The minimal diagnostic criteria are lower abdominal pain, cervical motion tenderness, and uterine/adenexal tenderness. In a patient at high risk, even partial fulfillment of criteria could warrant

beginning treatment. A patient that is not toxic in appearance, is tolerating PO, can keep a follow-up appointment, and can be relied on to be compliant with medication can be treated as an out-patient, even as an adolescent. If they need to be admitted because they can not meet the above, the recommendations are for Cefotetan or Cefoxitin PLUS Doxycycline; or Clindamycin PLUS Gentamicin. As you can see by the recommendations, coverage for Bacterial Vaginosis as the etiology of PID is something that should always be considered. This is of increased importance if the tests for GC and Chlamydia are negative.

### Herpes

Several different medications are available. For the 1<sup>st</sup> clinical episode of genital herpes, you can use: Acyclovir 400mg PO TID for 7-10 days, or Acyclovir 200mg PO Five times a day for 7-10 days, or Famciclovir 250mg PO TID for 7-10 days, or Valacyclovir 1 gram PO BID for 7-10 days. For recurrent outbreaks, treatment must be started within 24 hours of the first lesions appearing. It is best to give your patient a small supply to keep at home so that they can begin treatment without having to wait for an appointment. Options are: Acyclovir 400mg PO TID for 5 days, Acyclovir 800mg PO BID for 5 days, Valacyclovir 500mg PO BID for 3-5 days, or Valacyclovir 1 gram PO once a day for 5 days. Patients that have problems with frequent outbreaks, defined as more than 6 per year in the MMWR guidelines may benefit from daily suppressive therapy. Some physicians would place all patients on suppressive therapy for the first 6 to 12 months after a first outbreak, as that is the time they are most at risk for recurrence. HSV 2 is more likely to have recurrence than HSV 1, so testing can help guide your decision about risk of recurrent outbreaks. For suppressive therapy,

you can use: Acyclovir 400mg PO BID, Famciclovir 250mg PO BID, Valacyclovir 500mg PO once a day, or Valacyclovir 1 gram PO once a day.

### HPV

Genital warts have many treatment options. In the office, topical Podophyllin resin 10%-25%, or topical Trichloroacetic acid/ Bichloroacetic acid 80-90% can be applied. This can be repeated weekly as necessary. For patients that have recurrent HPV outbreaks, there are two options for home treatment. Podofilox 0.5% solution or gel applied with a cotton swab to visible warts twice a day for 3 days, followed by 4 days of no medicine. This can be repeated for up to four cycles (1 month). Imiquimod 5% cream applied once a day 3 times a week for up to 16 weeks. The areas should be washed with soap and water 6-10 hours after each application.

1. CDC. Sexually transmitted diseases treatment guidelines 2002. MMWR 2002;51 (No. RR-6) available on-line at [www.cdc.gov/std/treatment/](http://www.cdc.gov/std/treatment/)



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can make significant differences in outcome, the pediatrician has greater need still how to identify, assess and manage these children.

The diagnostic criteria for autism and its related disorders are found in the DSM IV under the grouping of Pervasive Developmental Disorders. Five disorders are listed: 1) Autistic Disorder, 2) Asperger Syndrome, 3) Rett Syndrome, 4) Childhood Disintegrative Disorder, and 5) Pervasive Develop-

mental Disorder – Not Otherwise Specified. We now know that Rett Syndrome is an X-linked dominant neurogenetic disorder caused by an abnormality in the MECP2 gene. Childhood Disintegrative Disorder is a rare regressive disorder occurring in older children and typically carries a very poor prognosis. In the 2000's the term Autistic Spectrum Disorder (ASD) has been used in policy and consensus statements. It refers to the three remaining disorders; Autism, Asperger, and PDD-NOS.

In autism (autistic disorder; AD), there is a triad of behavioral abnormalities. **The first is qualitative impairment in reciprocal social interactions or relatedness.** Abnormalities here involve impairment in the use of multiple nonverbal behaviors such as eye contact and eye gaze, gestures and body postures to regulate social interactions, poor peer relationships, lack of joint attention, and a lack of social emotional reciprocity, i.e. that sense of “connectedness” one has when interacting with another. Lack of joint attention refers to the ability to coordinate one’s own attention between an object and another person to indicate a need or share interest. For example, when a child points to an interesting object and says “Oh look Mommy!” and shifts their gaze between their mother and the object, they are demonstrating joint attention. Children typically develop these skills between 12 and 15 months. Abnormal development in joint attention skills appears to be universal and specific to ASDs. There is now data to suggest that the development of joint attention accurately predicts the development of functional language within a year.

**The second area of abnormality in autism involves qualitative impairments in communication.**

Here there may be a lack of meaningful language without attempts to compensate through gesture, or an

inability to sustain a conversation even though one has adequate language. There may be the use of unusual or repetitive language such as echolalia. Echolalia may be immediate or delayed. While children with simple delays in language may use immediate echolalia while trying to process what they have heard, delayed echolalia, e.g. repeating conversations or dialogue heard on a video the day before, is unusual. Autistic children may engage in both forms of echolalia. Lack of varied, spontaneous, make-believe or social imitative play appropriate to the child's developmental level is also included in this area.

**The third area of behavioral abnormality involves restricted, repetitive, stereotyped patterns of behavior, interest or activities.**

Children may stay occupied for prolonged periods playing with bits of string, spinning the wheels on toy cars or lining up objects. We saw an older boy who spent hours making detailed drawings of passenger jet planes, cockpits, and runway diagrams. Perhaps not too unusual until we found out his other interest was making equally detailed drawings of soda machines! Children may insist certain things be "just so" in a nonfunctional way; e.g. insisting the parent always take a certain way home and tantruming if this is not done. Children may be more interested in a certain part of toy rather than playing with the toy as it is intended. Included in this area too are unusual body movements and postures such as prolonged spinning, rocking, toe walking and unusual finger flicking behaviors.

Individuals with Asperger Syndrome (AS) are similar to those with autism, sharing both the deficits in social function, and the restrictive, repetitive, stereotyped

patterns of behavior, interest and activities. The DSM requires individuals who have AS to have "normal" early language although many feel a mild delay should not disqualify an individual from this diagnosis. Language in AS individuals is often described as professorial and pedantic. They often wish only to talk about their area of restricted interest, a habit which contributes significantly to their social problems. Problems with motor coordination are common. Importantly, these children have normal IQ's as opposed to the classic autistic child, the majority of whom are mentally retarded.

Pervasive Developmental Disorder – Not Otherwise Specified is a sub-threshold disorder invoked when a child clearly has deficits in the above areas, but does not meet specific criteria for one of the other diagnoses. Children are sometimes diagnosed with PDD – NOS and later found to have autism or AS as symptoms continue to develop.

**Increasing Prevalence**

Studies prior to 2000 all put the prevalence of autism at less than 1 per 1000. The most recent estimates however, have put the prevalence of autism (AD) at 1 per 500 and for ASD's overall at 3-5 per 1000. Some states have reported an increase of 200 to 900% for special education services for ASDs. Reasons for this increase are debated. The diagnostic criteria have broadened with each edition of the DSM resulting in more individuals meeting criteria. There has also been increased recognition of the disorder, and with the deinstitutionalization of individuals with mental retardation, greater numbers of autistic individuals live

in the community. These factors do not rule out however a true increase in prevalence.

**Etiology: Multifactorial**

Ten to fifteen percent of ASDs are associated with and/or caused by a known genetic or medical disorder. These include Fragile X syndrome, neurocutaneous disorders (tuberous sclerosis in particular), PKU, CHARGE association, as well as prenatal Rubella and CMV infections. About 7% of Down syndrome children are also autistic. The other 85 to 90% of autism occurs in the absence of a known underlying disorder. Family and twin studies have clearly shown a strong genetic component to this "idiopathic" autism. It is clear that multiple genes are involved in a process that may involve one or more regulator genes that are activated during brain development. Estimates range from 3 to 20 different genes being involved. Current "hot spots" include chromosome 6, 7 (multiple areas), 13q, 15, 16, 17, and 22. Most important to the clinician is that *the recurrence rate in children who have a sibling with an ASD is 3 to 7% or higher*

Environmental influences appear to play a part in some cases of autism. The prevalence of autism within the Brick Township is 7 per 1000, much higher than even the latest estimates. This area is located near the Metedeconk River where elevated levels of trihalomethanes were found and associated with a Superfund Waste Site. The evidence regarding environmental and genetic influences however, points towards in utero exposures and triggers. There is no conclusive evidence that the MMR vaccine causes autism. Nor is there any good data

to suggest thimerosal, a preservative previously used in vaccines, causes autism. Interestingly, we know that premature infants were exposed to relatively higher doses (based upon their smaller body weight) of thimerosal in their Hepatitis B vaccinations, and yet prematurity itself is not a risk factor for autism.

### The Pediatricians' Role

In May 2001 the AAP provided guidelines as to the role of the pediatrician in the diagnosis and management of ASDs in children. Accompanying the guideline was a very thorough technical report. This report, found on the AAP e-pages (see below), is a wealth of information on the screening, diagnosis and management of ASDs.

First and foremost, pediatricians need to listen to their parents' concerns when discussing a child's development. Studies have clearly shown that parents are reliable sources of information and their concerns need to be properly addressed. Pediatricians need to monitor all aspects of a child's development during well child care. A number of psychometrically sound, easy to administer instruments are now available. These include the Ages and Stages Questionnaire (used at BAMC and WHMC), the PEDS (Parent Evaluation of Developmental Status), and the Child Developmental Inventories among others. Pediatricians may wish to consider using a specific autism screening tool if they have raised concerns. The most well know of these is the Checklist for Autism in Toddlers (CHAT) which combines 9 questions with a 5 item observation/interaction section. The M-CHAT eliminates the observation section and adds additional questions. Both these instruments are available on the web ([www.firstsigns.org](http://www.firstsigns.org)). In the absence

of a screening instrument, one may ask specific questions which may include:

- “Does your child...
- ...not speak as well as his/her peers?
- ...have poor eye contact?
- ...not respond selectively to his/her name?
- ...act as if he/she is in their own world?
- ...seen to tune others out?
- ...not have a social smile that can be elicited reciprocally?
- ...seem unable to tell you what he or she wants, thus preferring to lead you by the hand, or get the desired object on their own?
- ...have difficulty following simple commands?
- ...not bring you things to simply show you?
- ...not point to interesting objects to direct your attention to objects of interest?
- ...have unusually long or severe temper tantrums?
- ...have repetitive, odd, or stereotypic behaviors?
- ...have an unusual attachment to inanimate objects especially hard ones? (e.g. flashlights, utensils, a chain as opposed to a blanket or stuffed animal)?
- ...prefer to play alone?
- ...demonstrate an inability to play with toys in the typical way?
- ...not engage in pretend play (if older than 2 years)?

If the answers to these tend to be “yes”, your ASD screening is suggestive of autism, or other suggestive abnormalities are found, the child should be referred to a specialist or multidisciplinary team for further evaluation. In addition the child should be simultaneously referred for Early Childhood Intervention services. Any child with a language delay needs an

evaluation by a speech pathologist (through ECI or otherwise) and full audiological evaluation.

In Part 2 of this series, we will review the diagnostic and medical work up and management of children with autistic spectrum disorders.

### Resources:

- 1) The Pediatricians Role in the Diagnosis and Management of Autistic Spectrum Disorder in Children., PEDIATRICS Vol 107 No.5 May 2001
- 2) The accompanying technical manual may be found at:

[www.pediatrics.org/cgi/content/full/107/5/e85](http://www.pediatrics.org/cgi/content/full/107/5/e85)



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His immunizations were up to date. His current medicines included Celexa 10 mg PO QHS, Risperdol 4 mg PO QHS, Depakote 100 mg PO QHS, and Lamictal 100mg PO QHS. He has no known allergies. On exam his vitals were: Temp 104.3(, P 104 , RR 36, and BP 111/62. His height and weight were at the 90th and 100th percentiles respectively. He was cooperative and alert. He had scleral injection and mild conjunctival inflammation bilaterally, with a mucopurulent eye discharge. His extra ocular movements were intact and his pupils were reactive. Of note his mouth was dry, with dry lips, some dried blood on the right buccal mucosa, a small area of peeling skin on his lower lip, pale gingiva, and an area of pale coloration on his left buccal mucosa. He had no lymphadenopathy. His chest was clear. Cardiovascular and abdominal exams were both normal. His cranial nerves II - XII were grossly intact, with no

**Table 8: LAMICTAL, Added to an ACD Regimen Containing VPM in Patients 2 to 12 Years of Age**

Weeks 1 and 2	0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.		
Weeks 3 and 4	0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet.		
Weight-based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of Lamictal 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
4.3 kg	14 kg	2 mg every other day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	48 kg	8 mg every day	16 mg every day

Usual maintenance dose: 1 to 6 mg/kg/day (maximum 288 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.

focal deficits. His skin had multiple areas of non-blanchable erythema, small papules on his chest and back, larger papules with serpiginous borders in the inguinal region and thighs, a few vesicles on his abdomen with the largest diameter approximately 1 mm, and no denuded skin. All of these lesions were non-tender, and there was no involvement of his palms and soles.

The differential diagnosis of this rash is broad, and includes Kawasaki's disease, mucositis, severe Herpes stomatitis, staphylococcal scalded skin syndrome, and multiple other causes. Labs that were drawn in the ED included a normal chemistry, UA, and LFTs, and did not help to narrow down the differential. But labs should not be necessary to make you think of Stevens-Johnson Syndrome, which is what this patient had. Stevens-Johnson Syndrome (SJS) is considered a hypersensitivity syndrome, which ranges on scale from Erythema Multiforme (EM) to the more severe forms, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). For EM, the more mild and common form, the onset of symptoms is usually acute and the disease is often recurrent. Etiologies that trigger it include infectious agents (especially HSV and mycoplasma infections), drugs, connective tissue diseases, physical agents,

malignancies, and in up to 50% of cases, idiopathic causes. The clinical manifestations include prodromal symptoms of malaise, fever, and itching or burning of the skin, followed by the appearance of characteristic target lesions and papules. Lesions usually evolve into target lesions in the first 24-48 hours. These lesions can also appear as dusky red, round, maculopapules. There is typically a symmetrical distribution on the backs of the hands, feet, and extensor surfaces of the forearms and legs. Bullae and erosive lesions may occur in the oral cavity. The trunk may be involved in severe cases. Lesions may heal in 1-2 weeks without any scarring except for hypopigmentation or hyperpigmentation as new crops of lesions appear. Entire episodes may last approximately 1 month. SJS and TEN are considered to be more severe forms of EM, however their exact classification is controversial. One method of classification defines SJS as mucosal erosions and epidermal detachment involving less than 10 % of the skin. There is some overlap of SJS/TEN when epidermal detachment and mucosal erosion is between 10% and 30%. These changes are classified as TEN when epidermal detachment is more than 30%. SJS can appear as a vesiculobullous disease of the skin, mouth, eyes, and genitals, although these lesions can often be flat,

atypical targets or purpuric maculae that are widespread or distributed on the trunk. It occurs most often in children and young adults. Cutaneous eruptions are preceded by URI symptoms. Bullae may occur suddenly anytime 1-14 days after the prodromal symptoms, and involve the mucous membranes of the mouth, nares, anorectal junction, vulvovaginal region, urethral meatus, and conjunctivae. The most characteristic feature is ulcerative stomatitis leading to hemorrhagic crusting. Corneal ulcerations can develop and may lead to blindness. Pulmonary involvement may be evident by a harsh, hacking cough and patchy changes on CXR. The prognosis with SJS is alarming. Mortality is approximately 10% with more extensive disease. High fevers may occur in the active stages. Although during the course of disease new crops of lesions may occur, the disease is generally self-limited and resolves in approximately 1 month if no complications occur. Oral lesions may continue for months. Severe ocular mucosal involvement may be a precipitating factor in the development of ocular cicatricial pemphigoid, a chronic scarring inflammation of the ocular mucosa that can lead to blindness. It may occur from a few months to years after the onset of SJS. Drugs are the most common cause of SJS. Well known associations have been described with Captopril, Etoposide, NSAIDS, Aspirin, Allopurinol, numerous anticonvulsants including Phenobarbital, Phenytoin, Lamotrigine, Valproic Acid and Carbamazepine. Also, antibiotics such as sulfonamides, penicillins, tetracyclines, cephalosporins, Isoniazid, and quinolones have been known to cause SJS. There are also numerous infectious etiologies including Mycoplasma pneumoniae, Mycobacterium tuberculosis, Group A Streptococci, EBV, Hepatitis B, enteroviruses, HSV 1 & 2, and numerous other causes. The

diagnosis is based on the clinical presentation along with a good history. Treatment is supportive. The inciting factor should be stopped or removed if possible. If lesions are progressing transfer to a PICU or burn unit should be done if available for optimal management. Ophthalmology should be consulted early for ocular lesions. These lesions need to be monitored closely as corneal scarring may lead to blindness. The use of corticosteroids is controversial. They may be associated with delayed recovery and significant side effects in children including increased morbidity and mortality, especially with sepsis. But they may also be lifesaving. Antihistamines can be used to control the itching. Lesions associated with HSV may be prevented by early use of Acyclovir. Finally, IVIG is now being investigated for use in the treatment of SJS. An important learning point for all pediatricians is that in this patient's case, one clue was available that could lead you to suspect SJS early on. His medication history revealed that he was on Lamotrigine and Valproic Acid, both known to be associated with SJS. Lamictal (Lamotrigine) is an antiepileptic drug of the phenyltriazine class. Its mechanism of action is unknown, but it is thought to effect sodium channels. Valproic acid decreases the clearance of Lamictal. Serious rashes requiring hospitalization have been associated with Lamictal. The incidence of these rashes (including SJS) is ~ 1% in the pediatric patient population and 0.3% in adults. Rare cases of death associated with these rashes (SJS/TEN) have been reported worldwide, but too few for an exact calculation. It has been suggested that the risk of rash increases with coadministration of Lamictal with Valproic Acid, exceeding the recommended initial dose of Lamictal, and exceeding the recommended dose escalation for Lamictal. However, cases have been reported

in the absence of the above. The recommended dosing guidelines from the PDR are listed below. As pediatricians we should all be aware of these guidelines since patients often come to us for renewals. Table 8 from PDR

### References

- 1) Carroll et al. Drug-Induced Hypersensitivity Syndrome in Pediatric Patients. *Pediatrics*. 2001; 108
- 2). Raugeau et al. Medication Use and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis. *New England Journal of Medicine*, 1995; 333 (24): 1600-1608. Wolkenstein, P. and Revuz, J. Toxic Epidermal Necrolysis. *Dermatologic Clinics*. 2000; 18
- 3). Yalcin, B. and Karaduman, A. Stevens-Johnson Syndrome Associated with Concomitant Use of Lamotrigine and Valproic Acid. *Journal of the American Academy of Dermatology*. 2000; 43 (5).



## Puberty and Its Disorders

Cydney L. Fenton  
MAJ, MC, USA  
Staff, Pediatric Endocrinology

### Introduction

**P**uberty is the physical maturation that is manifested by increased growth rate and appearance of secondary sexual characteristics. Disorders of the timing of puberty constitute a significant portion of referrals to our pediatric endocrinology clinic. This article is written to assist the general pediatrician in the recognition and evaluation of children who present

with abnormalities in the timing of their puberty. This article is not meant to be all inclusive and represents a brief overview of a complex physical process.

### Normal Puberty

#### Boys

Onset and duration of pubertal changes may vary considerably. The first sign of pubertal development in boys is testicular enlargement. The mean age for this first step is 11 years, development of pubic hair occurs approximately two years later. This is followed by a peak growth velocity of approximately 10.3 cm/yr. Growth ceases when the epiphyseal plates fuse at a bone age of 17 – 18 in boys. Puberty is considered abnormal if it begins before the age of 9 or does not begin before the age of 14 in boys.

#### Girls

The timing of puberty in young girls remains the subject of some controversy. The first sign of pubertal development in girls is breast enlargement. The mean age for this first step is 10 years, development of pubic hairs typically follows within the next 6 months. This is followed by a peak growth velocity of approximately 9 cm/yr. Menarche occurs approximately 2 years after thelarche, with cessation of growth and fusion of the epiphyseal plates at a bone age of 15. Fewer than 10% of girls start to menstruate before age 11 and 90% of all girls are menstruating before age 13.75. Puberty is considered abnormal if it begins before the age of 8 in girls. Delayed puberty should be considered if there is no breast development by age 13 or no menarche by age 15.

### Delayed Puberty

By definition, 2.5% of the

normal population will have the start of puberty more than 2 standard deviations beyond the mean. Most of these children will have constitutional delay of adolescence, the late bloomers. They must, however, be differentiated from children with pathology. Pubertal delay is classified based on the level of initial gonadotropin secretion.

### **Hypergonadotropic Hypogonadism**

These are disorders characterized by secondary gonadotropin increase. This is usually caused by end organ failure; i.e., problems with the gonads. Differential includes, but should not be limited to variants of ovarian and testicular dysgenesis, gonads that have been damaged by radiation and/or chemotherapy, androgen insensitivity certain steroid enzyme deficiencies, and other miscellaneous disorders. Girls with Turner Syndrome and boys with Klinefelter Syndrome are in this category secondary to ovarian and testicular failure, respectively.

### **Hypogonadotropic Hypogonadism**

These disorders are primary disorders of the hypothalamic-pituitary axis characterized decreased gonadotropin secretion. Differential diagnosis include children with other pituitary deficiencies, isolated growth hormone deficiency, Kallman and Prader-Willi Syndromes, hypothyroidism, glucocorticoid excess, and hyperprolactinemia. Children with constitutional delay will fit into this category.

### **Eugonadotropic Conditions**

These disorders mainly encompass patients with primary amenorrhea. These patients have normal onset of pubertal development but they never progress to menarche. The differential includes abnormalities of the Mullerian ducts, such as

absence of the uterus, vagina, or both. Some authors will include polycystic ovarian syndrome and hyperprolactinemia.

### **Evaluation**

A thorough history may reveal that the child with constitutional delay had a pattern of slow growth during childhood with progressive heights tracking along the lower limits of normal. Patients with hypogonadotropic hypogonadism tend to have normal growth during childhood but fail to develop the expected pubertal growth spurt. Family history, to include timing of pubertal onset in siblings, parents, and grandparents can provide target heights as well as a history of constitutional delay. The history of prior malignancies and treatment with chemotherapy or radiation exposure can provide a direction to your evaluation. A thorough review of systems related to gastrointestinal, cardiac, renal, thyroid, and central nervous system function should be reviewed.

Physical examination may also provide clues to the etiology of the delay. Boys with eunuchoidal body proportions may have Klinefelter Syndrome. The sense of smell should be evaluated, as patients with Kallman's may have anosmia or hyposmia. Pubertal staging with appropriate measurements of breast tissue and testicular size should be obtained. Children with Prader-Willi tend to be short, obese, with mild mental retardation and hypogonadism. Physical stigmata of Turner Syndrome should be sought for all short girls with pubertal delay. Cushing syndrome will present with pubertal delay and growth failure, but the patients should have physical stigmata of glucocorticoid excess. A goiter may signify hypothyroidism.

Laboratory and radiological

evaluation should proceed in an orderly fashion. The passage of time will help differentiate patients with constitutional delay, over those with significant pathology. A bone age is important for evaluation of continued growth potential and hypothalamic maturity. Pelvic ultrasonography is vital to detect the presence, absence, and size of Mullerian structures. Laboratory evaluation should include a measure of FSH and LH. This will help to establish if the patient has hypergonadal or hypogonadal hypogonadism. Thyroid functions tests, prolactin levels, and karyotype levels should be considered in all patients, as well as the measurement of testosterone and estradiol in boys and girls respectively.

### **Treatment**

The psychological effect of pubertal delay can be significant and may include symptoms of emotional tension and depression, psychosomatic complaints such as abdominal pain, feelings of inferiority, etc. Treatment options will depend on the etiology of the pubertal delay. Decreased bone mineral density is a potential complication of pubertal delay and delay in therapy. For boys with constitutional delay, testosterone therapy should not be considered much before a bone age of 12, assuming that the patients chronological age is greater than 14. Discussion with a pediatric endocrinologist should be considered prior to initiation of any therapy for pubertal delay.

*Part II will follow in a future issue of Pediatric News.*

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John Baker, M.D.  
Editor, *Pediatric News*  
Department of Pediatrics  
San Antonio Uniformed Services Pediatrics  
jabaker@texas.net