Movement Disorders II: Chorea, Dystonia, Myoclonus, and Tremor

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Cover: The artwork on the cover of this month's issue is by one of the winners of our 2009 Cover Art Contest, 6-year-old Emma Rethy of Leesburg, VA. Emma's pediatrician is Patricia Rappaport, MD.

Answer Key: 1. C; 2. C; 3. A; 4. D; 5. B; 6. B; 7. C; 8. B; 9. A; 10. C; 11. E; 12. B; 13. E

Atopic Dermatitis and Ichthyosis

Roselyn E. Epps

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Atopic Dermatitis and Ichthyosis

Roselyn E. Epps, MD*

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Dr Epps has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Identify the characteristic features of atopic dermatitis and the factors that worsen it.
2. Understand that children who have atopic dermatitis are prone to recurrent infections, particularly with *Staphylococcus aureus* and herpes simplex virus.
3. Know the signs of Wiskott-Aldrich syndrome.
4. Plan the appropriate treatment of atopic dermatitis (emollients, corticosteroids, antibiotics, and allergen elimination when appropriate).
5. Recognize ichthyosis vulgaris and know that ichthyosis commonly occurs in children who have atopic dermatitis.
6. List the effective therapies in the management of ichthyosis vulgaris.
7. Distinguish between tinea pedis and atopic dermatitis.
8. Discuss the relationship of atopic dermatitis and food allergies and how to evaluate a patient who has both.
9. Explain why children who have one component of atopy syndrome (allergic rhinitis, asthma, atopic dermatitis) have a threefold greater risk of developing a second component.

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, relapsing dermatosis that features dry skin (xerosis), pruritus, and a personal or family history of eczema, allergic rhinitis or allergies, or asthma. Children who have one component of the atopic triad (AD, asthma, allergic rhinitis) are three times as likely to develop a second component. There is no sex predilection, and the onset frequently is in infancy. Although many affected children outgrow the condition by age 5 years, AD may persist into adolescence and adulthood. A smaller percentage of patients experience the onset of AD as older children or in adulthood.

The incidence and prevalence of AD have increased in the United States and worldwide, particularly in developed nations. Fewer than 10% of children were affected in the 1970s, but recent epidemiologic studies estimate that 15% to 20% of children are diagnosed with AD. The reason for the increased rate is unknown. The "hygiene hypothesis" proposes that decreased exposure to infectious and biologic antigens may result in an increased response to environmental antigens or perhaps to decreased immune suppression. Additional research must be conducted to determine the reasons for the increased prevalence and to address the trend.

Pathophysiology

Manifestations of AD are believed to be due to the interaction of certain genes, the environment, and immunologic response to the environment and specific trigger factors. Patients who have AD may be considered to have systemic changes, not just manifestations in the skin. Susceptible individuals can react to internal and environmental triggers in certain target organs, not only resulting in skin eruptions, but also in asthma and allergic rhinitis. Patients may exhibit extrinsic immunoglobulin E (IgE)-mediated sensitization due to external antigens, with allergenic signs and elevated allergen-specific IgE, or intrinsic sensitization, without IgE-mediated sensitization.

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In acute AD lesions, T-helper 2 (TH2) cells are present in larger numbers than normal and have increased expression of specific cytokines that, in turn, stimulate B cells to produce IgE, resulting in peripheral eosinophilia. Cytokines and chemokines are released from cells in the skin, attracting other inflammatory cells and producing inflammatory mediators and reactions. Keratinocytes, Langerhans cells, endothelial cells, monocyte-macrophages, and eosinophils all play roles in the acute and chronic inflammation of AD.

Clinical Manifestations

Generally, the primary lesion is a red, rough, poorly defined dry papule or plaque. Scaling may be seen. There is no central clearing. In children of color or deep pigmentation, plaques can be papular or follicular, especially on the trunk or over the extensor areas of joints.

AD is diagnosed clinically and manifests particular patterns at different ages. Frequently, infants present with rough patches or plaques on the cheeks, the dorsa of the wrists, the ankles, and the lateral extremities. The perioral and diaper areas customarily are spared. After infancy, children develop flexural involvement, and the cheek areas improve. The neck, antecubital and popliteal fossae, and gluteal folds frequently are involved (Fig. 1).

Teenagers are more likely to experience eyelid eruptions. With age, the hands and feet also become more problematic, and AD may present as dyshidrotic eruptions. Any part of the body, from the scalp to the soles and including the lips and genitalia, may be affected at any age. Eruptions occur whether or not an offending factor or trigger is identified. Exacerbations and remissions are common and to be expected.

Secondary skin changes occur frequently. Oozing, weeping, and crust formation can develop, which may represent secondary infection. Hyperpigmentation as well as hypopigmentation and depigmentation (loss of pigmentation) can occur. Normal color of the skin usually returns when the signs and symptoms of AD resolve. Weeks to months may be required for the hyperpigmentation and hypopigmentation to resolve. If excoriations are deep or the inflammation is severe, scarring or depigmentation can be permanent.

Lichenification, a hallmark of AD, is thickening and accentuation of skin markings due to chronic scratching. Lichenified skin on the hands and feet is more likely to fissure. Excoriations are common, and some patients create erosions and deeper wounds by unrelenting, intense, repeated trauma. Repeated friction and trauma promote inflammation and trigger inflammatory reactions and pathways in affected skin. Lichenification also may occur in other dermatologic conditions that feature chronic scratching and pruritus.

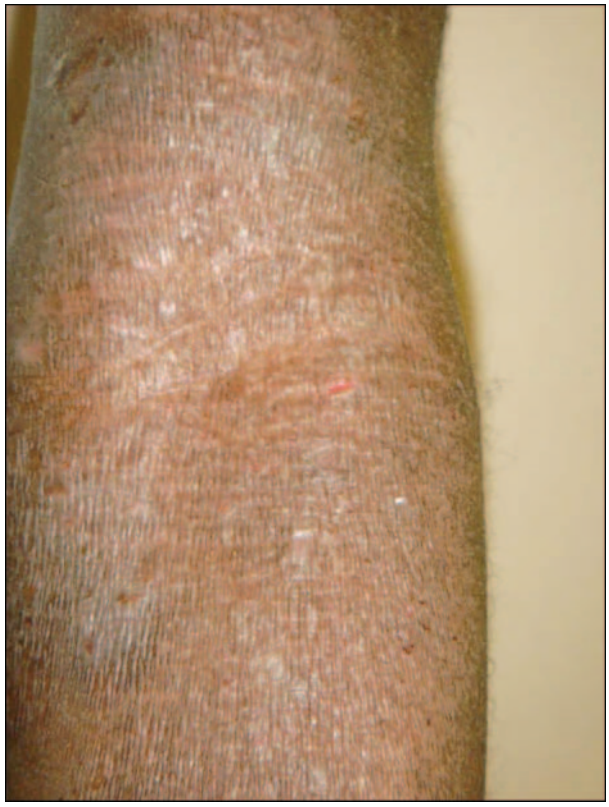

Figure 1. Atopic dermatitis often involves the antecubital fossa. Lichenification and excoriations are evident in this example.

Friction on the skin and scratching the skin are known to exacerbate pruritus and can initiate the "itch-scratch cycle," in which the child scratches, itching in the involved area increases, the child continues to scratch, and the cycle continues. Plaques, papules, and nodules can result because of the escalating "itch-scratch cycle."

Secondary Infection

Patients who have AD are more likely to develop skin and possibly systemic infections. One reason superinfection occurs more easily is due to altered skin barrier function, including apparent and imperceptible excoriations, fissures, and skin defects (Fig. 2). For patients who have AD, seemingly uninvolved skin is not normal. In addition to greater irritancy and dryness, there are immunologic differences in the type of TH2 cells and an increase in the number of TH2 cells within the skin. *Staphylococcus aureus* is an important cause of superinfection. *S aureus* colonization by age 6 months, with frequent

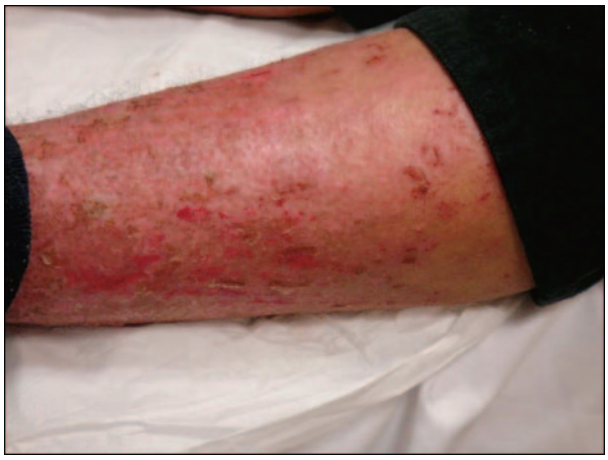

Figure 2. Atopic dermatitis of this leg shows erythema, excoriations, and scaling consistent with superinfection.

colonization during the first year after birth, is associated with an increased prevalence and severity of AD. Impaired skin barrier function, a defective host immune response, and increased synthesis of extracellular matrix adhesion substances promote *S aureus* colonization.

Exotoxins secreted by *S aureus* penetrate the skin barrier and stimulate T cells and antigen-presenting cells, thereby exacerbating and contributing to persistent skin inflammation. *S aureus* overgrowth and superinfection can result in flares, impetigo, folliculitis, cellulitis, abscesses, bacteremia, and sepsis. Methicillin-resistant *S aureus*, now more common in the community, can be particularly problematic for patients who have AD and their families. The patient's infection must be treated, and treating the family may be necessary to minimize the risk of AD exacerbation in the patient. The clinician should consider culturing the atopic patient who is febrile, is unresponsive to therapy, or shows an inadequate response to maximized treatment that includes antibiotic therapy. Other bacteria also may be cultured from the AD patient's wounds and should be treated accordingly.

Although patients who have AD develop bacterial infections, they also may acquire viral and fungal infections. Eczema herpeticum occurs when AD is superinfected with a herpesvirus, either herpes simplex virus or varicella-zoster virus. Vesicles develop on affected and apparently unaffected skin and can be very painful. When disseminated, there may be associated viremia, fever, and lymphadenopathy, and patients can become very ill. Ocular involvement may occur innocuously when the patient rubs his or her eyes. Acyclovir should be administered intravenously in critical disseminated infections or orally for localized, recurrent infections in patients who have AD. If herpesvirus infection involves the eye or periocular area, ophthalmology consultation is essential to manage herpes keratitis and to prevent permanent loss of vision.

Dermatophytes and yeast also can superinfect the skin. Patients who have AD can develop tinea capitis and tinea pedis, and it can be difficult at times to distinguish AD from tinea infection because both may involve pruritus, scaling, and inflammation. On physical examination, unlike AD, tinea pedis frequently develops in the toe web spaces (particularly the third and fourth). Tinea lesions frequently feature expanding plaques with central clearing and peripheral papules and scale. Potassium hydroxide slide examination of a sample taken from the skin from any affected body area, including the skin, the scalp, and hair, can help make the diagnosis.

Allergy and Environment

Allergic contact dermatitis can exacerbate AD. Common contact triggers include fragrances and preservatives in personal care products such as soaps, cleansers, shampoos, detergents, and certain emollients. Among other materials and substances that commonly elicit symptoms of allergic contact dermatitis are wool, nickel, synthetics, dyes, and rubber.

Physical and environmental factors also can play a role. Temperature changes between cold and hot environments (as when moving from an air conditioned enclosure to hot outdoor weather) or change of season can be problematic. Some children prefer warm or cool temperatures. Therefore, their dermatitis is milder in the summer or winter, respectively. Other environmental variables such as dust and mites, pollen, and ambient humidity can have an impact. Because sweating can produce pruritus and skin eruptions for some patients, treatment of AD may require modifying exercise regimens. Clothing tags, coarse fabrics, snug clothing, and footwear can worsen symptoms in a localized distribution. Emotional factors such as stress, anger, sleepiness, and boredom often increase pruritus.

The role of foods in causing AD can be significant for some children; food allergies can be present in up to 40% of patients who have AD. Symptoms include pruritus, urticaria, contact dermatitis, and exacerbation of AD as well as wheezing, asthma, and anaphylaxis. The symptoms can be immediate or delayed. Among the leading allergenic foods are milk and dairy products, eggs, wheat, soy, and peanuts. Some children outgrow allergies to particular foods, but peanuts and eggs are often the exception. Although some foods are difficult to avoid, the improved availability of nutritional information, di-

etary counseling, and food labeling helps families make proper dietary choices for children who have food allergies.

Allergy skin prick testing usually is more reliable after age 2 years; specific radioallergosorbent testing can be performed in infancy. The patient must not take oral antihistamines or steroid medications for several days before skin prick allergy testing; AD should be controlled as much as possible to allow proper evaluation while minimizing patient discomfort. Avoidance of allergenic substances identified by allergy testing occasionally benefits the patient who has AD, but AD can be exacerbated by unrelated factors while allergies are present. Allergy testing may be repeated and expanded if the patient does not improve after avoidance therapy.

Management

Treatment of AD requires a coordinated plan aimed at moisturizing dry skin, decreasing inflammation, treating any infections, and avoiding irritants and other factors associated with dermatitis flares. The regimen must be discussed with the family, patient, and clinicians to ensure compliance.

Bathing is an important aspect of general skin care for patients who have AD. Baths and showers should be brief and the water comfortably warm, never hot. After exposure to water, the skin should be patted or excess water brushed off of the skin before applying medication and moisturizer. Some patients improve and are maintained with daily or twice-daily bathing. Other patients experience drying and increased pruritus or discomfort with water contact, making infrequent bathing the required approach. In addition, during flares, some patients are unable to bathe or shower due to discomfort and pain. Bathing may be resumed when symptoms decrease.

Although not necessary, a variety of commercial products, including cleansers, soaps, oils, and oatmeal powders, can be combined with bath water. Fragrance-free soaps and cleansers are preferred, but which product benefits or is tolerated by each patient differs. The use of bubble bath, shampoo, and dishwater detergent to cleanse the body should be avoided. For some, dilute chlorine bleach baths are beneficial, particularly for children whose AD improves after swimming in chlorinated pools. One-quarter to one-half cup of bleach in the bathtub (24 gallons or a standard tub filled 4 to 6 inches) should create a sufficient concentration without bleaching or damaging linens. Dilute white vinegar, extra light olive oil, and other products also have been used for bathing.

Because the skin of patients who have AD is dry, the use of emollients is a cornerstone of therapy. Even without visible lesions, dry skin often is pruritic. Many products are available; no single emollient provides relief, moisturizes the skin, and improves skin barrier function for all patients. The medication vehicle (eg, cream versus ointment) and the presence of fragrance, preservatives, or other additives can affect the patient's response. Lotions, creams, ointments, and oils are composed of varying amounts of oil and water. Ointments are composed of more petroleum jelly, creams contain more water than oil, and lotions contain more water than cream. If the skin is excoriated or fissured, stinging or pain can occur from products containing more water. An optimal time for moisturizer application is immediately after the bath or shower. Many patients benefit from several emollient applications per day.

Topical corticosteroids have been a mainstay of AD therapy for approximately 50 years. Hydrocortisone (up to 1%) is available over the counter, and numerous prescription preparations are available (Table). Ointments, creams, lotions, gels, foams, and oil preparations are available. Different preparations deliver corticosteroid through the skin in varying potencies. If preparations are used sparingly and appropriately, adverse effects should be minimized. Adverse effects include skin atrophy, telangiectasias, striae, and systemic absorption. The use of potent and fluorinated corticosteroids on the face and intertriginous and diaper areas should be avoided due to increased absorption through thinner or occluded skin. Middle-strength to more potent corticosteroid medications may be required for treating lichenified areas or on the hands and feet due to the increased skin thickness and keratin of the skin layers.

Several clinical trials of topical corticosteroid use in the pediatric age group have been performed or are in progress; some topical corticosteroids are approved specifically for use in children and some infants. Many practitioners find topical corticosteroids useful to break the itch-scratch cycle, treat acute flares, and minimize symptoms of inflammation. When signs and symptoms improve, the frequency of topical corticosteroid application should be reduced while moisturizer use is continued. Continuous, prolonged application of topical corticosteroids also can produce tachyphylaxis or decreased effectiveness of the medication.

Oral corticosteroid therapy has limited use in treating AD. Although helpful for some severe flares, once therapy is discontinued, the rebound or subsequent flare that may occur might be more severe than the initial exacerbation and more difficult to control. Some patients become oral corticosteroid-dependent in their attempt to

Table. **Topical Corticosteroids Ranked Strongest (Class I) to Weakest (Class VII)**

	Medication	Available Formulation
Class I	Clobetasol propionate 0.05%	Cream, ointment, gel, foam
	Betamethasone dipropionate augmented 0.05%	Ointment
	Diflorasone diacetate 0.05%	Ointment
	Fluocinonide 0.01%	Ointment
	Halobetasol propionate 0.05%	Cream, ointment
Class II	Amcinonide 0.01%	Ointment
	Betamethasone dipropionate 0.05%	Ointment
	Betamethasone dipropionate augmented 0.05%	Cream
	Desoximetasone 0.25%	Cream, ointment
	Desoximetasone 0.05%	Gel
	Fluocinonide 0.05%	Cream, ointment, gel, solution
	Halcinonide 0.1%	Cream, ointment, solution
	Mometasone furoate 0.1%	Ointment
Class III	Amcinonide 0.1%	Cream, lotion
	Betamethasone valerate 0.1%	Ointment
	Desoximetasone 0.05%	Cream
	Fluocinonide emollient 0.05%	Cream
	Fluticasone propionate 0.005%	Ointment
	Halcinonide 0.1%	Solution
	Triamcinolone acetonide 0.1%	Ointment
Class IV	Betamethasone valerate 0.12%	Foam
	Fluocinonide acetonide 0.025%	Ointment
	Flurandrenolide 0.05%	Ointment
	Fluticasone propionate 0.05%	Cream
	Hydrocortisone valerate 0.2%	Ointment
	Mometasone furoate 0.1%	Cream, lotion
	Triamcinolone acetonide 0.1%	Cream, ointment
Class V	Betamethasone dipropionate 0.05%	Lotion
	Betamethasone valerate 0.1%	Cream
	Clocortolone pivalate 0.1%	Cream
	Desonide 0.05%	Ointment
	Fluocinolone acetonide 0.025%	Cream
	Flurandrenolide 0.05%	Cream
	Fluticasone propionate 0.01%	Oil
	Fluticasone propionate 0.05%	Cream
	Hydrocortisone butyrate 0.1%	Cream, ointment
	Hydrocortisone valerate 0.2%	Cream
	Prednicarbate 0.1%	Cream
	Triamcinolone acetonide 0.1%	Lotion
Class VI	Alclometasone 0.05%	Cream, ointment
	Betamethasone valerate 0.1%	Lotion
	Desonide 0.05%	Cream
	Fluocinolone acetonide 0.01%	Cream, lotion
	Hydrocortisone butyrate 0.1%	Solution
	Triamcinolone acetonide 0.1%	Cream
	Triamcinolone acetonide 0.025%	Cream, lotion
Class VII	Hydrocortisone acetonide, dexamethasone	Cream, ointment, lotion

Note: Vehicle affects medication potency for several products.

prevent flares and are more likely to develop adverse systemic effects such as hypothalamic-pituitary axis suppression, growth retardation, and cushingoid features.

Chronic, high-dose, or high-potency oral corticosteroid use has been shown to cause osteopenia or osteoporosis in children and adults. It is not known whether chronic intermittent topical corticosteroid use affects the bones of children. Some physicians give vitamin D and calcium supplementation to patients who have AD. Of note, the American Academy of Pediatrics has released new recommendations regarding vitamin D supplementation in children; the recommended minimum dose was doubled to 400 IU daily for infants and children. Clearly, corticosteroid use in children who have AD, the impact of therapy on bone health, and the role of vitamin D and calcium supplementation merit additional scientific study.

Topical calcineurin inhibitors are newer elements of the therapeutic armamentarium. Pimecrolimus 1% cream is approved for mild-to-moderate AD. Tacrolimus ointment is available in 0.03% and 0.1% strengths and is targeted for moderate-to-severe AD. Tacrolimus 0.03% and pimecrolimus are approved by the United States Food and Drug Administration for those ages 2 years and older; tacrolimus 0.1% is intended for those ages 15 years and older. Both medications can be used on any part of the body and are particularly beneficial for the eyelids, face, and intertriginous areas.

The most common adverse effects reported are burning at the site of application, headache, upper respiratory tract symptoms, cough, and pyrexia. In addition, exacerbation of viral infections, including herpesvirus infection, verrucae, and molluscum contagiosum, may be more likely in patients who use these products. A black box warning was placed on both medica-

tions, stating that long-term safety of topical calcineurin inhibitors has not been established and that these medications are not recommended for use in children younger than age 2 years. Additional therapeutic trials in children who have AD are planned and needed.

Several prescription topical nonsteroidal moisturizing creams have been approved for use in AD. Their purpose is to improve the hydrolipid layer and barrier function, relieve AD symptoms, and promote wound healing. They may be used alone or in combination with topical corticosteroids and calcineurin inhibitors. The nonsteroid creams Atopiclair® Nonsteroidal Cream (Graceway Pharmaceuticals, Bristol, Tenn.), Eletone® Cream (Ferndale Laboratories, Ferndale, Mich.), Epiceram® Skin Barrier Emulsion (Promius Pharmaceuticals, Bridgewater, NJ), and MimyX® Cream (Steifel Pharmaceuticals, Bristol, Tenn.) are approved for all ages, for use on any area of the body, and may be used two to three times a day. Zetania® cream (Tiber Laboratories, Suwanee, Ga.) is approved for children 2 years of age and older. Patients allergic to any components of the creams should avoid their use.

Oral antihistamine drugs have been prescribed for patients who have AD. Although not statistically proven to be useful for treating pruritus generally, oral antihistamines can be helpful for children who have an urticarial component or decreased or altered sleep patterns due to pruritus.

Wiscott–Aldrich Syndrome

Wiskott-Aldrich syndrome is one important condition to consider in patients who have AD. This X-linked recessive disorder features eczematous eruptions in association with thrombocytopenia and recurrent infections. Thrombocytopenic purpura and hemorrhagic events may occur. The identified Wiskott-Aldrich syndrome protein (*WASP*) gene codes for a cytoplasmic protein that has multiple functions. The impaired humoral immune response to polysaccharide antigens seen in patients who have Wiskott-Aldrich syndrome makes patients susceptible to bacteria such as *Streptococcus pneumoniae* and *Pneumocystis jiroveci* and, later, to viruses. After the second decade of life, these patients are at risk for developing leukemia and lymphoma.

Job Syndrome

Another important condition to consider is Job syndrome, or hyperimmunoglobulin E syndrome (HIES), which is defined by eczematous eruptions associated with IgE concentrations greater than 2,000 IU/mL and repeated skin and sinopulmonary infections. The classic autosomal dominant form is due to a mutation in the signal transducer and activator of the transcription 3 (*STAT3*) gene. Skin eruptions appear during the newborn period, with onset of infections during the first 3 postnatal months. Although the type of skin infection can vary, "cold" abscesses are typical and feature slight redness, no or low-grade fever, little systemic involvement, and minimal signs and symptoms, unlike abscesses seen in patients unaffected by HIES. Paronychiae and candidal infections are common. Although the eczematous symptoms usually resolve, the recurrent pulmonary infections due to *S aureus* and *Haemophilus influenzae* progress to chronic lung infections and subsequent lung changes. Of note, children who have AD can have very high concentrations of IgE; conversely, patients who have HIES can have normal IgE concentrations.

Ichthyosis

Ichthyosis represents a group of disorders that involves abnormal epidermal skin barrier function, keratinization, and desquamation. Multiple types of ichthyosis have been described. Initially defined descriptively, the disorders now can be distinguished by genetic, histologic, biochemical, and molecular methods.

Ichthyosis vulgaris (IV) is the most common type, with an incidence of 1 in 250. The onset is during infancy or childhood, not at birth. Inheritance can be autosomal dominant or sporadic, so patients have a varied presentation. IV usually presents as fine white scales on the skin, sparing the antecubital and popliteal fossae. Scaling is most obvious on the lateral lower legs (Fig. 3). Hyperlinearity is noted on the palms and soles. IV can be innocuous and appear as an isolated finding. The histopathology may show a thinned-to-absent granular layer and a compact superficial stratum corneum. However, a skin biopsy may not be diagnostic; microscopically, IV can look like normal skin. IV often improves with age, and manifestations in adulthood may be minimal.

There are many forms of ichthyosis, most of which are rare. Ichthyosis can be inherited in autosomal or X-linked patterns or by spontaneous mutation. Although IV is rather common, X-linked ichthyosis, lamellar ichthyosis, and harlequin fetus are rare, well-described forms (Fig. 4). Several syndromes and related conditions of note include ichthyosis as part of the clinical picture. KID syndrome is defined as keratitis, ichthyosis, and deafness. Netherton syndrome, also called ichthyosis linearis circumflexa, features congenital erythroderma as well as atopic dermatitis, hair shaft abnormalities, and high IgE concentrations.

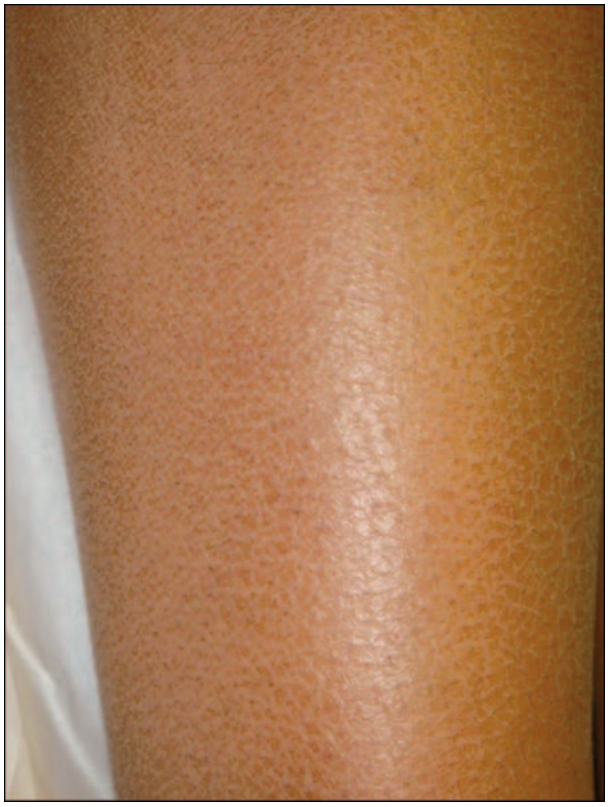

Figure 3. Ichthyosis vulgaris demonstrates fine, white scales.

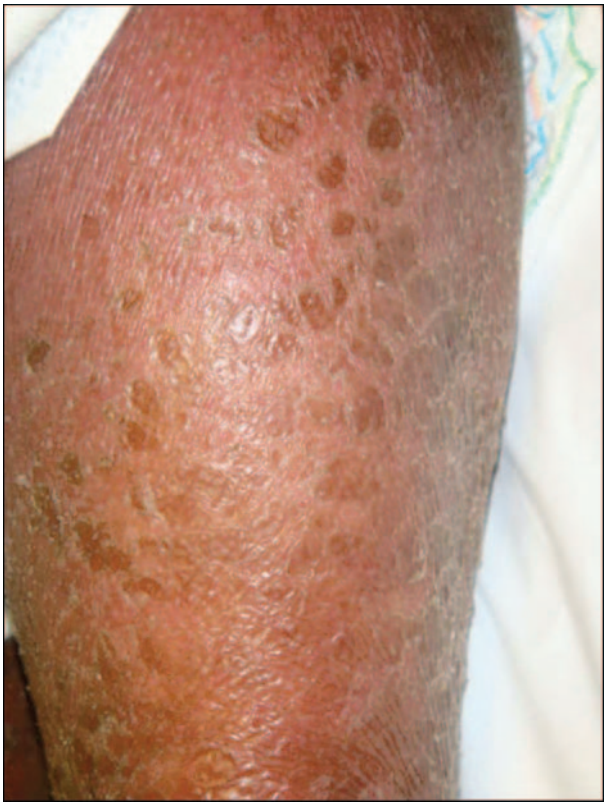

Figure 4. Lamellar ichthyosis features larger, platelike scales.

Management

Treatment of IV usually involves the use of topical salicylic acid; lactic acid; or urea in lotion, cream, or ointment form. These products moisturize, soften the skin, and aid in desquamation. For patients who have both IV and AD, these products are more likely to cause irritation. The products should be used cautiously in children because total body application can result in systemic absorption and serious adverse effects. Salicylic acid, in particular, should be used in children after 1 year of age and then with caution due to risks of salicylate toxicity.

Research

Significant research has been performed in IV, AD, and related disorders. IV often coexists with AD, and research has shown a genetic basis for this association in certain populations. Gene mutations in keratin proteins alter skin barrier function. Most important, the *FLG* gene produces profilaggrin, and filaggrin is critical for AD expression. Multiple international and familial studies have shown that *FLG* mutations in patients who have AD alter normal skin formation, function, and hydration and result in severe AD, as well as asthma associated with AD.

The mutation for IV also has been identified. Studies have shown that Northern European patients who have IV have a statistically significant increased risk for developing AD as well. Also, patients who have both IV and AD have a statistically significant increased risk for developing asthma. Overall, there is strong evidence for a genetic and molecular basis for the association of IV and AD. More studies are in progress and are necessary for

Summary

- Based on strong research evidence and consensus, a multifaceted, individualized approach to treatment benefits patients who have atopic dermatitis and includes bathing, emollients, topical anti-inflammatory medications, allergen avoidance, and the use of antistaphylococcal antibiotics and antihistamines when clinically indicated. (1)(2)
- Based on strong research evidence, mutations in the *FLG* gene cause ichthyosis vulgaris, resulting in alterations in the skin protein filaggrin. (3)(4)
- Based on strong research evidence, atopic dermatitis is associated with certain populations who have ichthyosis vulgaris. (5)(6)(7)

elucidating the role of altered cutaneous barrier function in AD and IV.

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PIR Quiz

Quiz also available online at http://wwwpedsinreview.aappublications.org.

5. Infants who have atopic dermatitis often have clinical features that are different from those of older affected children. Which of the following areas of the body is *more* likely to be affected in infants?

   A. Antecubital fossae.
   B. Cheeks.
   C. Eyelids.
   D. Genitals.
   E. Neck.

6. You are evaluating a 4-year-old boy who has a history of atopic dermatitis that usually affects his feet and popliteal fossae. He complains of itching and increased rash on his feet for several weeks. His mother feels that his atopic dermatitis is flaring up. Which of the following features makes a diagnosis of tinea pedis *more* likely than an exacerbation of atopic dermatitis?

   A. Erythema.
   B. Lesions in web spaces.
   C. Plaques without central clearing.
   D. Pruritus.
   E. Scaling.

7. Which of the following treatments is recommended for all patients who have atopic dermatitis?

   A. Complete avoidance of eggs and peanuts.
   B. Daily prophylactic topical antibiotic cream.
   C. Emollient application after a bath or shower.
   D. Frequent bathing with hot water.
   E. Periodic oral corticosteroid courses.

8. You are evaluating a 4-month-old boy during a health supervision visit. His mother complains that he is "always sick," and she is concerned about his constant "dry skin." She describes three upper respiratory tract infections and one episode of pneumonia that required hospitalization in the past 2 months. On physical examination, you note numerous scaly, erythematous patches on the infant's face and the extensor surfaces of his arms and legs. In addition, an erythematous diaper rash with satellite lesions is visible. You obtain a complete blood count, which reveals eosinophilia but no other abnormalities. Which of the following is the *most* likely diagnosis?

   A. Allergic contact dermatitis.
   B. Hyper-immunoglobulin E syndrome.
   C. Lamellar ichthyosis.
   D. Tinea corporis.
   E. Wiskott-Aldrich syndrome.

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Developmental Milestones: Motor Development

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Developmental Milestones: Motor Development

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Objectives

After completing this article, readers should be able to:

1. Identify the milestones for gross and fine motor development.
2. Recognize the child whose development falls outside of the expected range.
3. Describe the sequences involved in gross and fine motor development.

This is the first of three articles on developmental milestones; the second and third articles will appear in the September and November 2010 issues of Pediatrics in Review, *respectively.*

Introduction

Infancy and childhood are dynamic periods of growth and change. Neurodevelopmental and physical growth proceed in a sequential and predictable pattern that is intrinsically determined. Skills progress from cephalic to caudal; from proximal to distal; and from generalized, stimulus-based reflexes to specific, goal-oriented reactions that become increasingly precise. As one clinician has stated, "infants [and children] are very orderly in their ways; they actually behave [and develop] according to laws that can be explored, discovered, confirmed, reconfirmed, and celebrated." (1) By convention, these neurodevelopmental "laws" or sequences often are described in terms of the traditional developmental milestones.

Milestones provide a framework for observing and monitoring a child over time. According to recent American Academy of Pediatrics and *Bright Futures* guidelines, pediatricians should incorporate developmental surveillance at every health supervision visit. Surveillance involves analyzing the milestones in the context of a child's history, growth, and physical examination findings to recognize those who may be at risk for developmental delay. A thorough understanding of the normal or typical sequence of development in all domains (gross motor, fine motor, problem-solving, receptive language, expressive language, and social-emotional) allows the clinician to formulate a correct overall impression of a child's true developmental status. However, it must be emphasized that even experienced pediatricians cannot rely solely on their knowledge of the milestones to identify children who have developmental concerns. Developmental screening using validated and standardized tools should occur at the 9-month, 18-month, and 30-month (or 24-month) health supervision visits or whenever surveillance uncovers a concern.

Although neurodevelopment follows a predictable course, it is important to understand that intrinsic and extrinsic forces produce individual variation, making each child's developmental path unique. Intrinsic influences include genetically determined attributes (eg, physical characteristics, temperament) as well as the child's overall state of wellness. Extrinsic influences during infancy and childhood originate primarily from the family. Parent and sibling personalities, the nurturing methods used by caregivers, the cultural environment, and the family's socioeconomic status with its effect on resources of time and money all play a role in the development of children. Developmental theory has, itself, developed as clinicians have tried to grapple with which influence is more predominant.

The focus of this series of articles is to help the clinician frame general concepts of development according to the developmental streams rather than highlight developmental

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abnormalities. The milestones cited are, on average, those at the 50th percentile for age. By understanding what is "normal" or typical, the clinician can appreciate more keenly what is abnormal or delayed. This article concentrates on normal motor development, with a brief mention about specific "red flags" that should alert clinicians to potential motor developmental problems. The second article in the series discusses cognitive and language development. The final article addresses the development of social-emotional skills. An all-inclusive table of milestones is provided in this first article as a reference (Table 1) both in print and online; Table 1 appears online only in the September and November articles.

Gross Motor Milestones

The ultimate goal of gross motor development is to gain independent and volitional movement. During gestation, primitive reflexes develop and persist for several months after birth to prepare the infant for the acquisition of specific skills. These brainstem and spinal reflexes are stereotypic movements generated in response to specific sensory stimuli. Examples include the Moro (Fig. 1), asymmetric tonic neck (ATNR) (Fig. 2), and positive support reflexes (Fig. 3). As the central nervous system matures, the reflexes are inhibited to allow the infant to make purposeful movements. For example, during the time when the ATNR persists, an infant is unable to roll from back to front, bring the hands to midline, or reach for objects. This reflex disappears between 4 and 6 months of age, the same time that these skills begin to emerge. The Moro reflex interferes with head control and sitting equilibrium. As this reflex lessens and disappears by 6 months of age, the infant gains progressive stability in a seated position (Fig. 4).

In addition to primitive reflexes, postural reactions, such as righting and protection responses, also begin to develop after birth. These reactions, mediated at the midbrain level, interact with each other and work toward the establishment of normal head and body relationship in space. Protective extension, for example, allows the infant to catch him- or herself when falling forward, sideways, or backwards (Fig. 5). These reactions develop between 6 and 9 months, the same time that an infant learns to move into a seated position and then to hands and knees. Soon afterward, higher cortical centers mediate the development of equilibrium responses and permit the infant to pull to stand by 9 months of age and begin walking by 12 months. Additional equilibrium responses develop during the second year after birth to allow for more complex bipedal movements, such as moving backward, running, and jumping.

During the first postnatal year, an infant thus moves from lying prone, to rolling over, to getting to hands and knees, and ultimately to coming to a seated position or pulling to stand (Fig. 6). Within the framework of Back to Sleep guidelines, infants must have age-appropriate and safe opportunities for "tummy time" to promote the development of these important prone-specific milestones. It is important to note that crawling is not a prerequisite to walking; pulling to stand is the skill infants must develop before they take their first steps. The ultimate goal of this timeframe is to develop skills that allow for independent movement and freedom to use the hands to explore, manipulate, and learn from the environment.

Gross motor development in subsequent years consists of refinements in balance, coordination, speed, and strength. The wide-based, slightly crouched, staccato gait of a 12-month-old evolves into a smooth, upright, and narrow-based style. The arms change from being held abducted and slightly elevated for balance to swinging in a reciprocal fashion as the gait reaches an adult pattern by age 3 years. Similarly, running develops soon after walking, starting as a stiff-legged approximation and changing into a well-coordinated movement that includes rapid change of direction and speed by 18 months of age.

Simultaneous use of both arms or legs occurs after successful use of each limb independently. At age 2 years, a child can kick a ball, jump with two feet off the floor, and throw a big ball overhand. Milestones for succeeding ages reflect progress in the length of time, number of repetitions, or the distance each task can be performed successfully. By the time a child starts school, he or she is able to perform multiple complex gross motor tasks simultaneously (such as pedaling, maintaining balance, and steering while on a bicycle).

Fine Motor Milestones

Fine motor skills relate to the use of the upper extremities to engage and manipulate the environment. They are necessary for a person to perform self-help tasks, to play, and to accomplish work. Like all developmental streams, fine motor milestones do not proceed in isolation but depend on other areas of development, including gross motor, cognitive, and visual perceptual skills. At first, the upper extremities play an important role in balance and mobility. Hands are used for support, first in the prone position and then in sitting. Arms help with rolling over, then crawling, then pulling to stand. Infants begin to use their hands to explore, even when in the supine position. When gross motor skills have developed such that the

Table 1. Developmental Milestones

Age	Gross Motor	Fine Motor	Self-Help	Problem-solving	Social/Emotional	Receptive Language	Expressive Language
1 month	• Chin up in prone position • Turns head in supine position	• Hands fisted near face	• Sucks well	• Gazes at black-white objects • Follows face	• Discriminates mother's voice • Cries out of distress	• Startles to voice/sound	• Throaty noises
2 months	• Chest up in prone position • Head bobs when held in sitting position	• Hands unfisted 50% • Retains rattle if placed in hand • Holds hands together	• Opens mouth at sight of breast or bottle	• Visual threat present • Follows large, highly contrasting objects • Recognizes mother	• Reciprocal smiling: responds to adult voice and smile	• Alerts to voice/sound	• Coos • Social smile (6 weeks) • Vowel-like noises
3 months	• Props on forearms in prone position • Rolls to side	• Hands unfisted 50% • Inspects fingers • Bats at objects	• Brings hands to mouth	• Reaches for face • Follows objects in circle (in supine position) • Regards toys	• Expression of disgust (sour taste, loud sound) • Visually follows person who is moving across a room	• Regards speaker	• Chuckles • Vocalizes when talked to
4 months	• Sits with trunk support • No head lag when pulled to sit • Props on wrists • Rolls front to back	• Hands held predominately open • Clutches at clothes • Reaches persistently • Plays with rattle	• Briefly holds onto breast or bottle	• Mouths objects • Stares longer at novel faces than familiar • Shakes rattle • Reaches for ring/rattle	• Smiles spontaneously at pleasurable sight/sound • Stops crying at parent voice • To and fro alternating vocalizations	• Orients head in direction of a voice • Stops crying to soothing voice	• Laughs out loud • Vocalizes when alone
5 months	• Sits with pelvic support • Rolls back to front • Anterior protection • Sits with arms supporting trunk	• Palmar grasps cube • Transfers objects: hand-mouth-hand • Holds hands together • Reaches/grasps dangling ring	• Gums/mouths pureed food	• Turns head to look for dropped spoon • Regards pellet or small cracker	• Recognizes caregiver visually • Forms attachment relationship to caregiver	• Begins to respond to name	• Says "Ah-goo" • Razzes, squeals • Expresses anger with sounds other than crying
6 months	• Sits momentarily propped on hands • Pivots in prone • In prone position, bears weight on 1 hand	• Transfers hand-hand • Rakes pellet • Takes second cube and holds on to first • Reaches with one hand	• Feeds self crackers • Places hands on bottle	• Touches reflection and vocalizes • Removes cloth on face • Bangs and shakes toys	• Stranger anxiety (familiar versus unfamiliar people)	• Stops momentarily to "no" • Gestures for "up"	• Reduplicative babble with consonants • Listens, then vocalizes when adult stops • Smiles/vocalizes to mirror
7 months	• Bounces when held • Sits without support steadily • Lateral protection • Puts arms out to sides for balance	• Radial-palmar grasp	• Refuses excess food	• Explores different aspects of toy • Observes cube in each hand • Finds partially hidden object	• Looks from object to parent and back when wanting help (eg, with a wind-up toy)	• Looks toward familiar object when named • Attends to music	• Increasing variety of syllables
8 months	• Gets into sitting position • Commando crawls • Pulls to sitting/kneeling position	• Bangs spoon after demonstration • Scissor grasp of cube • Takes cube out of cup • Pulls out large peg	• Holds own bottle • Finger feeds Cheerios® or string beans	• Seeks object after it falls silently to the floor	• Lets parents know when happy versus upset • Engages in gaze monitoring: adult looks away and child follows adult glance with own eyes	• Responds to "Come here" • Looks for family members, "Where's mama?"... etc	• Says "Dada" (nonspecific) • Echolalia (8 to 30 months) • Shakes head for "no"

(continued)

Table 1. Developmental Milestones—continued

Age	Gross Motor	Fine Motor	Self-Help	Problem-solving	Social/Emotional	Receptive Language	Expressive Language
9 months	• "Stands" on feet and hands • Begins creeping • Pulls to stand • Bear walks (all four limbs straight)	• Radial-digital grasp of cube • Bangs two cubes together	• Bites, chews cookie	• Inspects bell • Rings bell • Pulls string to obtain ring	• Uses sounds to get attention • Separation anxiety • Follows a point, "Oh look at . . ." • Recognizes familiar people visually	• Enjoys gesture games • Orients to name well • Orients to bell	• Says "Mama" (nonspecific) • Nonreduplicative babble • Imitates sounds
10 months	• Creeps well • Cruises around furniture using two hands • Stands with one hand held • Walks with two hands held	• Clumsy release of cube • Inferior pincer grasp of pellet • Isolates index finger and pokes	• Drinks from cup held for child	• Uncovers toy under cloth • Pokes at pellet in bottle • Tries to put cube in cup, but may not be able to let go	• Experiences fear • Looks preferentially when name is called	• Enjoys peek-a-boo • Waves "bye-bye" back	• Says "Dada" (specific) • Waves "bye-bye"
11 months	• Pivots in sitting position • Cruises furniture using one hand • Stands for a few seconds • Walks with one hand held	• Throws objects • Stirs with spoon	• Cooperates with dressing	• Finds toy under cup • Looks at pictures in book	• Gives objects to adult for action after demonstration (lets adult know he or she needs help)	• Stops activity when told "no" • Bounces to music	• Says first word • Vocalizes to songs
12 months	• Stands well with arms high, legs splayed • Posterior protection • Independent steps	• Scribbles after demonstration • Fine pincer grasp of pellet • Holds crayon • Attempts tower of two cubes	• Finger feeds part of meal • Takes off hat	• Rattles spoon in cup • Lifts box lid to find toy	• Shows objects to parent to share interest • Points to get desired object (proto-imperative pointing)	• Follows one-step command with gesture • Recognizes names of two objects and looks when named	• Points to get desired object (proto-imperative pointing) • Uses several gestures with vocalizing (eg, waving, reaching)
13 months	• Walks with arms high and out (high guard)	• Attempts to release pellet in bottle	• Drinks from cup with some spilling	• Dangles ring by string • Reaches around clear barrier to obtain object • Unwraps toy in cloth	• Shows desire to please caregiver • Solitary play • Functional play	• Looks appropriately when asked, "Where's the ball?"	• Uses three words • Immature jargoning: inflection without real words
14 months	• Stands without pulling up • Falls by collapse • Walks well	• Imitates back and forth scribble • Adds third cube to a two-cube tower • Puts round peg in and out of hole	• Removes socks/shoes • Chews well • Puts spoon in mouth (turns over)	• Dumps pellet out of bottle after demonstration	• Points at object to express interest (proto-declarative pointing) • Purposeful exploration of toys through trial and error	• Follows one-step command without gesture	• Names one object • Points at object to express interest (proto-declarative pointing)
15 months	• Stoops to pick up toy • Creeps up stairs • Runs stiff-legged • Walks carrying toy • Climbs on furniture	• Builds three- to four-cube tower • Places 10 cubes in cup • Releases pellet into bottle	• Uses spoon with some spilling • Attempts to brush own hair • Fusses to be changed	• Turns pages in book • Places circle in single-shape puzzle	• Shows empathy (someone else cries, child looks sad) • Hugs adult in reciprocation • Recognizes without a demonstration that a toy requires activation; hands it to adult if can't operate	• Points to one body part • Points to one object of three when named • Gets object from another room upon demand	• Uses three to five words • Mature jargoning with real words
16 months	• Stands on one foot with slight support • Walks backwards • Walks up stairs with one hand held	• Puts several round pegs in board with urging • Scribbles spontaneously	• Picks up and drinks from cup • Fetches and carries objects (same room)	• Dumps pellet out without demonstration • Finds toy observed to be hidden under layers of covers • Places circle in form board	• Kisses by touching lips to skin • Periodically visually relocates caregiver • Self-conscious; embarrassed when aware of people observing	• Understands simple commands, "Bring to mommy" • Points to one picture when named	• Uses 5 to 10 words

(continued)

Table 1. Developmental Milestones—continued

Age	Gross Motor	Fine Motor	Self-Help	Problem-solving	Social/Emotional	Receptive Language	Expressive Language
18 months	• Creeps down stairs • Runs well • Seats self in small chair • Throws ball while standing	• Makes four-cube tower • Crudely imitates vertical stroke	• Removes garment • Gets onto adult chair unaided • Moves about house without adult	• Matches pairs of objects • Replaces circle in form board after it has been turned around (usually with trial and error)	• Passes M-CHAT • Engages in pretend play with other people (eg, tea party, birthday party) • Begins to show shame (when does wrong) and possessiveness	• Points to two of three objects when named • Points to three body parts • Points to self • Understands "mine" • Points to familiar people when named	• Uses 10 to 25 words • Uses giant words (all gone, stop that) • Imitates environmental sounds (eg, animals) • Names one picture on demand
20 months	• Squats in play • Carries large object • Walks downstairs with one hand held	• Completes round peg board without urging • Makes five- to six-cube tower • Completes square peg board	• Places only edibles in mouth • Feeds self with spoon entire meal	• Deduces location of hidden object • Places square in form board	• Begins to have thoughts about feelings • Engages in tea party with stuffed animals • Kisses with pucker	• Points to three pictures • Begins to understand her/him/me	• Holophrases ("Mommy?" and points to keys, meaning: "These are Mommy's keys.") • Two-word combinations • Answers requests with "no"
22 months	• Walks up stairs holding rail, putting both feet on each step • Kicks ball with demonstration • Walks with one foot on walking board	• Closes box with lid • Imitates vertical line • Imitates circular scribble	• Uses spoon well • Drinks from cup well • Unzips zippers • Puts shoes on partway	• Completes form board	• Watches other children intensely • Begins to show defiant behavior	• Points to four to five pictures when named • Points to five to six body parts • Points to four pieces of clothing when named	• Uses 25 to 50 words • Asks for more • Adds one to two words/week
24 months	• Walks down stairs holding rail, both feet on each step • Kicks ball without demonstration • Throws overhand	• Makes a single-line "train" of cubes • Imitates circle • Imitates horizontal line	• Opens door using knob • Sucks through a straw • Takes off clothes without buttons • Pulls off pants	• Sorts objects • Matches objects to pictures • Shows use of familiar objects	• Parallel play • Begins to mask emotions for social etiquette	• Follows two-step command • Understands me/you • Points to 5 to 10 pictures	• Two-word sentence (noun + verb) • Telegraphic speech • Uses 50+ words • 50% intelligibility • Refers to self by name • Names three pictures
28 months	• Jumps from bottom step with one foot leading • Walks on toes after demonstration • Walks backward 10 steps	• Strings large beads awkwardly • Unscrews jar lid • Turns paper pages (often several at once)	• Holds self and verbalizes toilet needs • Pulls pants up with assistance	• Matches shapes • Matches colors	• Reduction in separation anxiety	• Understands "just one"	• Repeats two digits • Begins to use pronouns (I, me, you) • Names 10 to 15 pictures
30 months	• Walks up stairs with rail, alternating feet • Jumps in place • Stands with both feet on balance beam • Walks with one foot on balance beam	• Makes eight-cube tower • Makes a "train" of cubes and includes a stack	• Washes hands • Puts things away • Brushes teeth with assistance	• Replaces circle in form board after it has been turned around (little or no trial and error) • Points to small details in pictures	• Imitates adult activities (eg, sweeping, talking on phone)	• Follows two prepositions: "put block in . . . on box" • Understands actions words: "playing . . . washing . . . blowing"	• Echolalia and jargoning gone • Names objects by use • Refers to self with correct pronoun • Recites parts of well-known story/fills in words
33 months	• Walks swinging arms opposite of legs (synchronous gait)	• Makes 9- to 10-cube tower • Puts six square pegs in pegboard • Imitates cross	• Toilet trained • Puts on coat unassisted	• Points to self in photos • Points to body parts based on function ("What do you hear with?")	• Begins to take turns • Tries to help with household tasks	• Understands three prepositions • Understands dirty, wet • Points to objects by use: "ride in . . . put on feet . . . write with"	• Gives first and last name • Counts to 3 • Begins to use past tense • Enjoys being read to (short books)

(continued)

Table 1. Developmental Milestones—continued

Age	Gross Motor	Fine Motor	Self-Help	Problem-solving	Social/Emotional	Receptive Language	Expressive Language
3 years	• Balances on one foot for 3 seconds • Goes up stairs, alternating feet, no rail • Pedals tricycle • Walks heel to toe • Catches ball with stiff arms	• Copies circle • Cuts with scissors: side-to-side (awkwardly) • Strings small beads well • Imitates bridge of cubes	• Independent eating • Pours liquid from one container to another • Puts on shoes without laces • Unbuttons	• Draws a two- to three-part person • Understands long/short, big/small, more/less • Knows own gender • Knows own age • Matches letters/numerals	• Starts to share with/without prompt • Fears imaginary things • Imaginative play • Uses words to describe what someone else is thinking ("Mom thought I was asleep")	• Points to parts of pictures (nose of cow, door of car) • Names body parts with function • Understands negatives • Groups objects (foods, toys)	• Uses 200+ words • Three-word sentences • Uses pronouns correctly • 75% intelligibility • Uses plurals • Names body parts by use • Asks to be read to
4 years	• Balances on one foot 4 to 8 seconds • Hops on one foot two to three times • Standing broad jump: 1 to 2 feet • Gallops • Throws ball overhand 10 feet • Catches bounced ball (4½ yrs)	• Copies square • Ties single knot • Cuts 5-inch circle • Uses tongs to transfer • Writes part of first name • Imitates gate with cubes	• Goes to toilet alone • Wipes after bowel movement • Washes face/hands • Brushes teeth alone • Buttons • Uses fork well	• Draws a four- to six-part person • Can give amounts (usually less than 5) correctly • Simple analogies: – dad/boy: mother/??? – ice/cold: fire/??? – ceiling/up: floor/??? • Points to five to six colors • Points to letters/numerals when named • Rote counts to 4 • "Reads" several common signs/store names	• Deception: interested in "tricking" others and concerned about being tricked by others • Has a preferred friend • Labels happiness, sadness, fear, and anger in self • Group play	• Follows three-step commands • Points to things that are the same versus different • Names things when actions are described (eg, swims in water, you cut with it, it's something you read, it tells time . . .) • Understands adjectives: bushy, long, thin, pointed	• Uses 300 to 1,000 words • Tells stories • 100% intelligibility • Uses "feeling" words • Uses words that tell about time
5 years	• Walks down stairs with rail, alternating feet • Balances on one foot >8 seconds • Hops on one foot 15 times • Skips • Running broad jump 2 to 3 feet • Walks backward heel-toe • Jumps backward	• Copies triangle • Puts paper clip on paper • Can use clothes-pins to transfer small objects • Cuts with scissors • Writes first name • Builds stairs from model	• Spreads with knife • Independent dressing • Bathes independently	• Draws an 8- to 10-part person • Gives amounts (<10) • Identifies coins • Names letters/numerals out of order • Rote counts to 10 • Names 10 colors • Uses letter names as sounds to invent spelling • Knows sounds of consonants and short vowels by end of kindergarten • Reads 25 words	• Has group of friends • Apologizes for mistakes • Responds verbally to good fortune of others	• Knows right and left on self • Points to different one in a series • Understands "er" endings (eg, batter, skater) • Understands adjectives: busy, long, thin, pointed • Enjoys rhyming words and alliterations • Produces words that rhyme • Points correctly to "side," "middle," "corner"	• Repeats six- to eight-word sentence • Defines simple words • Uses 2,000 words • Knows telephone number • Responds to "why" questions • Retells story with clear beginning, middle, end
6 years	• Tandem walks	• Builds stairs from memory • Draws diamond • Writes first and last name • Creates and writes short sentences • Forms letters with down-going and counterclockwise strokes • Copies flag	• Ties shoes • Combs hair • Looks both ways at street • Remembers to bring belongings	• Draws a 12- to 14-part person • Number concepts to 20 • Simple addition/subtraction • Understands seasons • Sounds out regularly spelled words • Reads 250 words by end of first grade	• Has best friend of same sex • Plays board games • Distinguishes fantasy from reality • Wants to be like friends and please them • Enjoys school	• Asks what unfamiliar words mean • Can tell which words do not belong in a group	• Repeats 8- to 10-word sentences • Describes events in order • Knows days of the week • 10,000 word vocabulary

Figure 1. Moro reflex. This reflex occurs spontaneously to loud noises or by simply holding the supine infant's hand and releasing the hand suddenly. Classically, the reflex is elicited while holding the infant supine, with the head dropped slightly backward. This produces sudden extension and abduction of the upper extremities with hands open, followed by flexion of the upper extremities to midline (the "startle reflex").

infant is more stable in upright positions and can move into them easily, the hands are free for more purposeful exploration.

At birth, infants do not have any apparent voluntary use of their hands. They open and close them in response to touch and other stimuli, but movement otherwise is dominated by a primitive grasp reflex. Because of this, infants spend the first 3 months after birth "contacting" objects with their eyes rather than their hands, fixating on faces and objects and then visually tracking objects. Gradually, they start to reach clumsily and bring their hands together. As the primitive reflexes decrease, infants begin to prehend objects voluntarily, first using the entire palm toward the ulnar side (5 months) and then predominantly using the radial aspect of the palm (7 months). At the same time, infants learn to release objects voluntarily. In the presence of a strong grasp reflex, objects must be removed forcibly from an infant's grasp or drop involuntarily from the hand. Voluntary release is seen as the infant learns to transfer objects from one hand to the other, first using the mouth as an intermediate stage (5 months) and then directly hand-to-hand (6 months).

Between 6 months and 12 months of age, the grasp evolves to allow for prehension of objects of different shapes and sizes (Fig. 7). The thumb becomes more involved to grasp objects, using all four fingers against the thumb (a "scissors" grasp) at 8 months, and eventually to just two fingers and thumb (radial digital grasp) at

Figure 2. Asymmetric tonic neck reflex (ATNR). The sensory limb of the ATNR involves proprioceptors in the cervical vertebrae. With active or passive head rotation, the baby extends the arm and leg on the face side and flexes the extremities on the contralateral side (the "fencer posture"). There also is some subtle trunk curvature on the contralateral side produced by mild paraspinous muscle contraction.

9 months. A pincer grasp emerges as the ulnar fingers are inhibited while slightly extending and supinating the wrist. Voluntary release is awkward at first, with all fingers extended. By 10 months of age, infants can release a cube into a container or drop things onto the floor. Object permanence reinforces the desire to practice this skill over and over. Intrinsic muscle control develops to allow the isolation of the index finger, and infants will poke their fingers into small holes for exploration. By 12 months of age, most infants enjoy putting things into containers and dumping them out repeatedly. They also can pick up small pieces of food with a mature pincer grasp and bring them to their mouths.

As infants move into their second year, their mastery of the reach, grasp, and release allows them to start using objects as tools. Fine motor development becomes more closely associated with cognitive and adaptive development, with the infant knowing both what he or she wants to

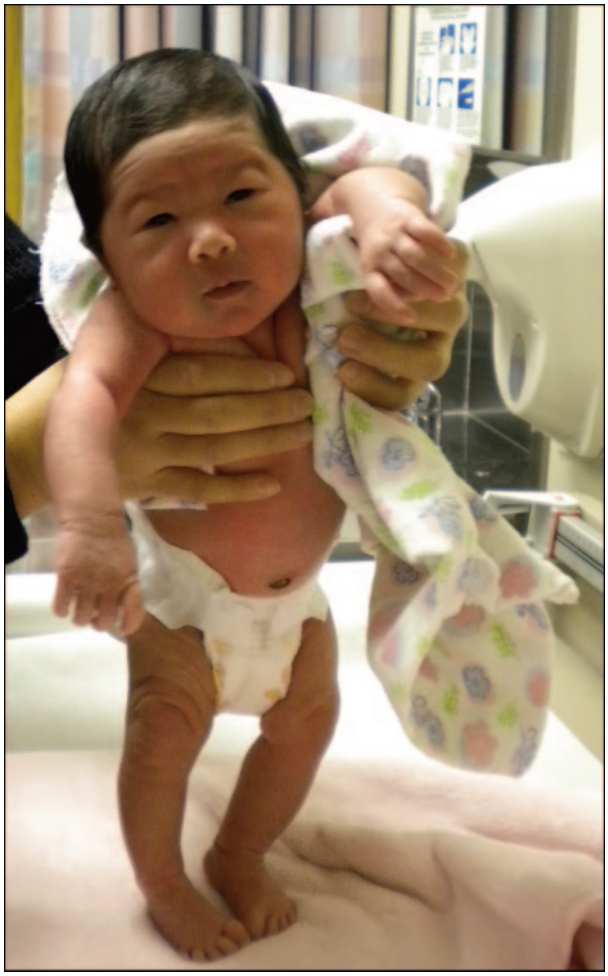

Figure 3. Positive support reflex. With support around the trunk, the infant is suspended, then lowered to touch the feet gently on a flat surface. This produces reflex extension at the hips, knees, and ankles so the infant stands up, completely or partially bearing weight. Mature weight-bearing lacks the rigid quality of this primitive reflex.

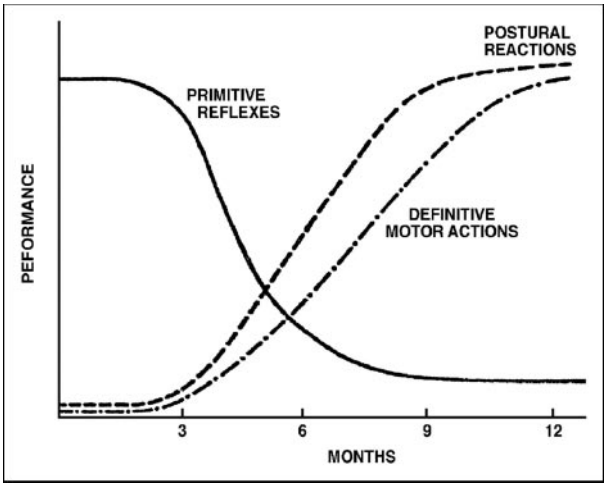

Figure 4. The declining intensity of primitive reflexes and the increasing role of postural reactions represent at least permissive, and possibly necessary, conditions for the development of definitive motor reactions. Reproduced with permission from Johnson CP, Blasco PA. Infant growth and development. *Pediatr Rev.* 1997;18:225–242.

do and how he or she can accomplish it. Intrinsic muscle refinement allows for holding flat objects, such as crackers or cookies. By 15 months of age, voluntary release has developed further to enable stacking of three to four blocks and releasing small objects into containers. The child starts to adjust objects after grasping to use them properly, such as picking up a crayon and adjusting it to scribble spontaneously (18 months of age) and adjusting a spoon to use it consistently for eating (20 months of age).

In subsequent years, fine motor skills are refined further to draw, explore, problem-solve, create, and perform self-help tasks. By age 2 years, children can create a six-block tower, feed themselves with a spoon and fork, re-

Figure 5. Lateral protection. In the seated position, the child is pushed gently but rapidly to one side. The reaction is present if the child puts out his or her hand to prevent a fall.

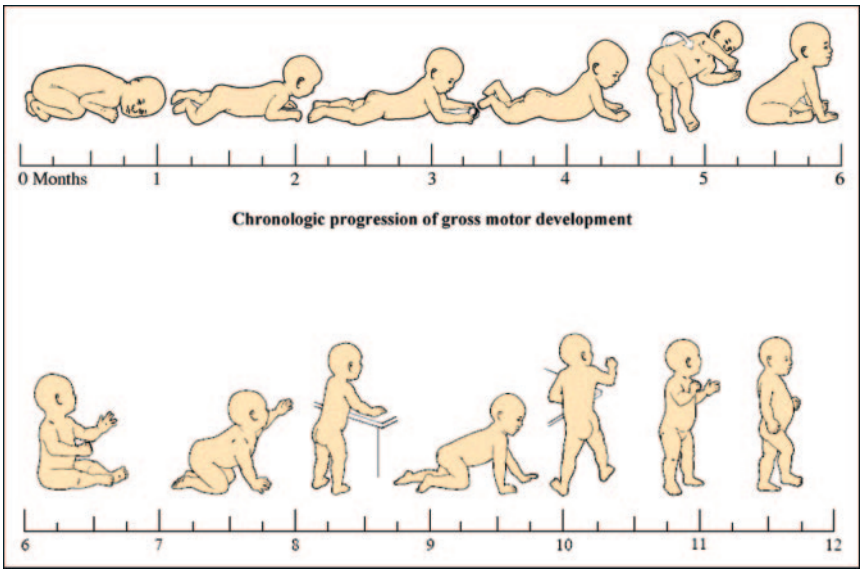

Figure 6. Chronologic progression of gross motor development during the first 12 postnatal months. Reproduced with permission from Johnson CP, Blasco PA. Infant growth and development. *Pediatr Rev.* 1997;18:224–242.

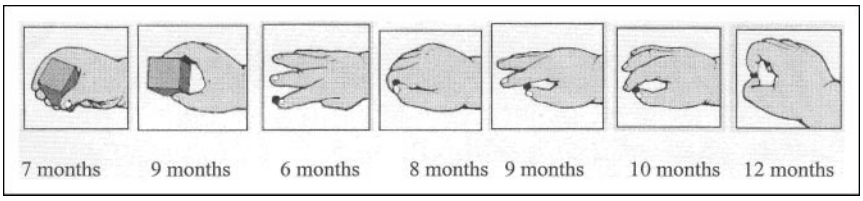

Figure 7. Development of pincer grasp. Illustrations from the Erhardt developmental prehension. In Erhardt RP. *Developmental Hand Dysfunction: Theory Assessment, Treatment.* 2nd ed. San Antonio, Tex: Therapy Skill Builders; 1994. Reprinted with permission.

Table 2. Motor Red Flags

Age	Red Flag
4 months	Lack of steady head control while sitting
9 months	Inability to sit
18 months	Inability to walk independently

move clothing, and grasp and turn a door knob. They have sufficient control of a crayon to imitate both vertical and horizontal lines. In-hand manipulation skills permit them to rotate objects, such as unscrewing a small bottle cap or reorienting a puzzle piece before putting it in place. They are able to wash and dry their hands. By 36 months of age, they can draw a circle, put on shoes, and stack 10 blocks. They make snips with scissors by alternating between full-finger extension and flexion. Their grasp and in-hand manipulation skills allow them to string small beads and unbutton clothes.

At age 4 years, a palmar tripod grasp allows for finer control of pencil movements, and the child can copy a cross, a square, and some letters and numerals and can draw a figure of a person (the head and a few other body parts). Scissor skills have progressed to permit the cutting of a circle. When a child reaches the age of 5 years, he or she can dress and undress independently, brush the teeth well, and spread with a knife. More precise in-hand manipulation skills enable the child to cut a square with mature scissor movements (independent finger use) and to print his or her own name and copy a triangle using a mature tripod pencil grasp (using the fingers to move the pencil rather than the forearm and wrist).

Developmental Red Flags

As the clinician performs developmental surveillance, the absence of certain key milestones in a patient should raise the level of concern. Table 2 lists the developmental red flags specific to the motor domain. If one of these red flags is discovered, a medical and more thorough developmental evaluation is warranted.

Although reported in this article in isolation, motor skills development overlaps significantly with the other streams of development.

Summary

- The development of motor skills is critical for a child to move independently and to interact with his or her environment meaningfully and usefully. Skills develop in a cephalic-to-caudal progression and from proximal to distal. Thus, consistent head support occurs before voluntary control of arms and legs, and large muscle control of the upper arms occurs before small, intrinsic muscle control in the hands.
- Skills also progress from generalized responses to stimuli (primitive reflexes) to goal-oriented, purposeful actions with ever-increasing precision and dexterity.

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Suggested Reading

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PIR Quiz

Quiz also available online at http://pedsinreview.aappublications.org.

1. An 18-month-old girl is seen for a health supervision visit. Her mother has no concerns regarding her daughter's development. Her growth parameters are at the 25th percentile. She walks well, climbs onto her mother's lap, and whispers a few words to her mother. The *best* next step in the evaluation of this child's development is:

   A. Full developmental surveillance.
   B. Further evaluation of language skills.
   C. Implementation of a developmental screening tool.
   D. Review of developmental milestones with the mother.
   E. Scheduling of a visit for full developmental assessment.

2. A 6-month-old infant is unable to roll from back to front or bring hands to midline. The *most* likely cause of this infant's difficulty is:

   A. Absence of lateral protection postural reaction.
   B. Absence of protective extension reaction.
   C. Persistence of asymmetric tonic neck reflex.
   D. Persistence of Moro reflex.
   E. Persistence of positive support reflex.

3. A 15-month-old typically developing girl is able to release cubes into a cup and has a mature fine pincer grasp. She *most* likely also is able to:

   A. Build a tower of three blocks.
   B. Copy a vertical line.
   C. Feed herself with a spoon and fork.
   D. Put on her shoes.
   E. Turn a doorknob.

4. An 18-month-old typically developing boy can walk well and run. He *most* likely also is able to:

   A. Jump with two feet off the ground.
   B. Kick a ball.
   C. Pedal a tricycle.
   D. Stoop and pick up a toy.
   E. Toe-walk.

Developmental Milestones: Motor Development

R. Jason Gerber, Timothy Wilks and Christine Erdie-Lalena

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Movement Disorders II: Chorea, Dystonia, Myoclonus, and Tremor

Jonathan W. Mink and Samuel H. Zinner

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Movement Disorders II:
Chorea, Dystonia, Myoclonus, and Tremor

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Author Disclosure
Drs Mink and Zinner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives
After completing this article, readers should be able to:

1. Identify the important distinguishing features of chorea, dystonia, myoclonus, and tremor.
2. Recognize important causes of chorea, dystonia, myoclonus, and tremor.
3. Describe treatment approaches for chorea, dystonia, myoclonus, and tremor.
4. Discuss common drug-induced movement disorders and their treatments.

Introduction
In a previous article, (1) we considered the two most common movement disorders in children: tics and stereotypies. Although less common, chorea, dystonia, myoclonus, and tremor are not rare in children. Therefore, it is important for the pediatric clinician to be able to recognize and distinguish these movement disorders. The first step in diagnosis and treatment is to identify and classify the disorders. In this article, we review these and drug-induced movement disorders. Drug-induced movement disorders fall into the same phenomenologic categories (chorea, dystonia, myoclonus, and tremor) but often are considered as a separate entity because of their specific causes and treatments.

Chorea
Definitions
Chorea is characterized by frequent, brief, unpredictable, purposeless movements that tend to flow from body part to body part chaotically and unpredictably. The movements are less sustained than those of dystonia but are more sustained and less "shocklike" than myoclonus. Low-amplitude chorea may cause an individual to appear fidgety. Large-amplitude chorea, sometimes termed "ballismus," can occur as dramatic flinging limb movements. Choreic movements (ie, characterized by chorea) can be sudden and jerky or can be more continuous and flowing. In the latter case, the term choreoathetosis is used. The term "choreiform" often is used to describe the minimal twitching or "piano playing" movements seen in many otherwise healthy young children when their arms are extended during the neurologic examination. The difference between "choreic" and "choreiform" in clinical usage is based on amplitude differences only and not on other characteristics of the movements. We prefer not to use the term "choreiform" but rather the more inclusive term "minimal chorea." (For examples of chorea, view the first three video segments in the data supplement.)

Causes
Chorea can be classified by cause into primary and secondary disorders. Primary chorea is uncommon in childhood. Primary causes include benign familial (hereditary) chorea and Huntington disease. However, Huntington disease rarely presents in childhood with chorea; juvenile-onset Huntington disease usually is characterized by parkinsonism and dystonia. Most

Abbreviations

ARF:	acute rheumatic fever
ASO:	antistreptolysin O
CSF:	cerebrospinal fluid
DRD:	dopa-responsive dystonia
GABHS:	group A beta-hemolytic *Streptococcus*
GTPCH:	guanosine 5′-triphosphate cyclohydrolase
MERRF:	myoclonic epilepsy and ragged-red fiber disease
NMS:	neuroleptic malignant syndrome
SC:	Sydenham chorea
SLE:	systemic lupus erythematosus
TD:	tardive dyskinesia
TH:	tyrosine hydroxylase

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chorea in childhood is due to other disorders. More than 100 causes of secondary chorea have been identified, but in most of those disorders, chorea is not the only sign or symptom. The most common cause of secondary chorea in childhood is acute rheumatic fever (ARF). Other important causes include systemic lupus erythematosus (SLE), cardiac surgery ("post-pump chorea"), and perinatal hypoxia-ischemia. A more extensive list of causes is shown in Table 1. A diagnostic strategy based on the more likely causes, with an emphasis on treatable causes, is shown in Table 2.

Sydenham Chorea (Rheumatic Chorea)

Chorea is one of the major Jones criteria for the diagnosis of ARF. The presence of chorea without any other criteria is sufficient to make the diagnosis of ARF. Although it is widely accepted that chorea can follow group A beta-hemolytic *Streptococcus* (GABHS) infection, it often is hard to demonstrate the antecedent infection. Depending on the series, 10% to 40% of children who have ARF have chorea. Sydenham chorea (SC) is most common in children 5 to 15 years old. There is a 2:1 female predominance after age 10 years. SC begins several weeks to several months after a GABHS infection. The onset of symptoms usually is insidious, with gradually progressive clumsiness and behavior change, usually including emotional lability. After a week or more, choreic movements become more obvious and typically become generalized. The chorea usually is asymmetric and, in rare cases, can be unilateral. The chorea commonly is accompanied by hypotonia and dysarthria. Classically described findings also include the "spooning sign" caused by hyperextension at the metacarpophalangeal joints; the "milkmaid's grasp," a sign of chorea that is detected by having the patient squeeze the examiner's fingers in a sustained manner, due to choreic intrusions and motor impersistence (ie, inability to maintain a posture), which are felt by the examiner as continuous fluctuation of the grasp; and the "darting tongue," due to choreic movements of the tongue and motor impersistence. Some children also display "hung-up" tendon jerk reflexes (ie, brisk reflex followed by a slowed return to the neutral position).

Behavioral changes may be striking and include impulsivity, aggression, and obsessive-compulsive behaviors. The natural history of SC is weeks to months of a waxing and waning course, with ultimate resolution of the chorea. Some individuals have behavioral changes that persist for months. Chorea relapse can occur with or without subsequent GABHS infection, and increased risk of relapse is associated with pregnancy (chorea gravidarum) and oral contraceptives.

Table 1. Causes of Secondary Chorea

Metabolic
• Hypo/hypernatremia
• Hypo/hyperglycemia
• Hypocalcemia
• Hyperthyroidism
• Wilson disease
Perinatal Hypoxia-Ischemia
Paraneoplastic
Infectious/Postinfectious
• Epstein-Barr virus infection
• Human immunodeficiency virus infection
• Acute rheumatic fever
• Viral encephalitis
Chorea gravidarum
Cardiac Surgery ("post-pump chorea")
Psychogenic
Vascular
• Antiphospholipid antibody syndrome
• Stroke
• Global hypoxia
• Moyamoya syndrome
• Systemic lupus erythematosus
Toxins
• Manganese
• Methanol
• Carbon monoxide
Heredodegenerative disease
• Ataxia telangiectasia
• Niemann-Pick disease type C
• Gangliosidoses
• Lesch-Nyhan disease

The diagnosis of SC is based on clinical history and physical examination findings but can be supported by laboratory data. However, laboratory data should not be viewed as confirmatory. Most children who have SC have positive serology (antistreptolysin O [ASO] and anti-DNase B antibodies) for GABHS, but more than 25% are serologically negative. Conversely, ASO titers can be elevated in children who do not have ARF. There is no correlation between titers and the severity of the chorea. Most children who develop SC have negative throat

Table 2. Diagnostic Testing in Chorea

- Throat culture
- Antistreptolysin O titer (ASO)
- AntiDNase B titer
- Electrocardiography
- Echocardiography
- Thyroid function tests
- Complete blood count
- Antinuclear antibody
- Erythrocyte sedimentation rate
- Magnetic resonance imaging of brain
- Serum ceruloplasmin concentration
- Antiphospholipid/anticardiolipin antibodies
- Urine drug screen
- Urine human chorionic gonadotropin concentration

Other testing for rare diseases is based on the presence of other symptoms and clinical suspicion. If results of the listed tests are normal, referral to a neurologist is recommended.

cultures for GABHS, but a positive culture result requires acute treatment. Magnetic resonance imaging scans may show signal abnormalities in the basal ganglia, but no sensitive or specific diagnostic tests for SC exist. The presence of carditis or other manifestations of ARF supports the diagnosis of SC. Every child believed to have SC should have an evaluation for rheumatic heart disease. Depending on the series, 40% to 75% of children who develop SC have carditis. Arthritis is less common.

Treatment of SC consists of secondary prevention, symptomatic treatment of chorea, and immune modulation. All children diagnosed as having SC, even in cases of isolated chorea, should be treated with penicillin, according to American Academy of Pediatrics guidelines. (2) An appropriate alternative may be selected for children who have penicillin allergies. Penicillin or an acceptable alternative is effective as secondary prevention of recurrent chorea but more importantly, reduces the likelihood that future GABHS infections will cause carditis and permanent valvular damage. Current recommendations in the United States are for treatment until age 21 years, regardless of the age of onset of the chorea.

Symptomatic treatment of SC depends on the impairment or disability associated with the chorea. In many cases, the chorea causes only mild disability, and symptomatic treatment is not required because SC usually is self-limited. When symptomatic treatment is desired, referral to a neurologist is recommended. Antiepileptic medications such as carbamazepine or valproate can be effective and usually are associated with fewer adverse effects than phenothiazines or butyrophenones. Benzodiazepines also may be beneficial. Symptomatic treatment for 2 to 4 months generally is sufficient. There have been no controlled studies of long-term outcomes of these treatments compared with placebo.

Based on the pathophysiology of SC, it is reasonable to consider using immune-modulating therapies to shorten the course of illness. According to one randomized, blinded, placebo-controlled study, (3) a 4-week course of oral prednisone (2 mg/kg daily) followed by a taper reduced the duration of chorea and accelerated the reduction in symptoms. Weight gain was substantial by the end of 2 months, and long-term outcome, including recurrence rates, was not different between groups. Other studies have been less conclusive. Because long-term outcome appears to be no different whether or not patients are treated with steroid medications, this treatment should be reserved for those who have severe chorea unresponsive to symptomatic treatment.

Chorea in Systemic Lupus Erythematosus

Chorea is an uncommon manifestation of SLE but can be the presenting symptom. When chorea is the sole manifestation of SLE, it can remain so for years. Although fewer than 10% of children who have SLE have chorea, about 50% of individuals who have chorea due to SLE are younger than 16 years of age. The presence of neurologic manifestations such as chorea in SLE conveys a less favorable prognosis. The diagnosis and treatment of SLE is beyond the scope of this review. When chorea is due to SLE, treatment of the underlying SLE is indicated. Additional symptomatic treatment of the chorea may be indicated if it is bothersome. Haloperidol has been reported to be effective for SLE chorea, but the other previously described treatments described for SC also may be effective.

Dystonia

Definitions

Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. There are several classification schemes for dystonia, based on age of onset, cause, or body part affected (Table 3). Primary dystonias are those disorders in which dystonia is either the only feature or the primary feature, and the cause either is a specific genetic mutation or is unknown. Secondary dystonias are those disorders in which the dystonia is due to another identifiable cause.

Focal dystonia occurs when only a single body part is affected. Almost any part of the body can be affected.

Table 3. Classification of Dystonia

Age of Onset
• Childhood
• Adulthood
Cause
• Primary (Idiopathic)
• Secondary
Somatic Distribution
• Segmental
• Multifocal
• Hemi
• Generalized

Examples of focal dystonia include torticollis and writer's cramp. Segmental dystonia refers to involvement of two or more adjacent body parts; multifocal dystonia describes involvement of multiple nonadjacent body parts. Hemidystonia affects only one side of the body, and generalized dystonia involves the entire body. Note that these classification schemes overlap. Childhood onset of primary generalized dystonia typically starts in an extremity and commonly progresses to generalized involvement with involuntary twisting of nearly all parts of the body.

Clinical Features

Dystonia has several characteristic clinical features. Dystonia commonly is triggered or exacerbated by attempted voluntary movement and may fluctuate in occurrence and severity over time. Dystonic contractions resolve during sleep. The dystonic posturing may occur only with selected movements and paradoxically not with others that may use the same muscles. For example, walking forward may elicit severe lower extremity and truncal twisting, yet walking backward, running, or swimming may be completely normal. Individuals who have dystonia often find that touching one part of the body may relieve the dystonic spasms; this phenomenon is called a sensory trick or geste antagoniste. For example, rubbing the back of the hand may diminish hand dystonia. (For an example of a patient who demonstrates dystonia, view the fourth segment of the video in the data supplement.)

Causes

Historically, dystonia has been divided into primary (idiopathic) and secondary causes. A full discussion of the many causes of dystonia is beyond the scope of this review. The two most important types of primary dystonia in children are dopa-responsive dystonia (DRD) and idiopathic torsion dystonia associated with the *DYT1* mutation. Other important causes of secondary dystonia in children are listed in Table 4.

Dopa-responsive Dystonia

DRD is a syndrome characterized by childhood onset and progressive dystonia that has a sustained dramatic response to low doses of levodopa. DRD also is known as hereditary progressive dystonia with diurnal fluctuations or Segawa syndrome. DRD typically presents with a gait disturbance due to foot dystonia starting between 1 and 12 years of age. In untreated older children, diurnal fluctuation develops, with worsening of symptoms toward the end of the day and marked improvement in the morning. Such diurnal fluctuation usually is not apparent in younger children. In late adolescence or early adulthood, features of parkinsonism can develop.

There are two major forms of DRD: a more common autosomal dominant form due to deficiency of guanosine 5′-triphosphate (GTP) cyclohydrolase (GTPCH)

Table 4. Causes of Secondary Dystonia in Children

Heredodegenerative Disorders
• Ataxia telangiectasia
• Gangliosidoses
• Glutaric aciduria
• Huntington disease
• Lesch-Nyhan disease
• Metachromatic leukodystrophy
• Methylmalonic acidemia
• Mitochondrial disorders
• Niemann-Pick disease type C
• Pantothenate kinase-associated neurodegeneration (PKAN)*
• Wilson disease
Drugs/Toxins (see Table 6)
Psychogenic
Structural Brain Lesions
• Acute disseminated encephalomyelitis
• Perinatal hypoxia-ischemia
• Stroke
• Tumor

*Also known as Hallervorden-Spatz syndrome.

and a relatively uncommon autosomal recessive form caused by a deficiency in tyrosine hydroxylase (TH). Both forms produce dopamine deficiency without loss of nigrostriatal dopamine neurons. A few clinical differences may help distinguish TH deficiency from GTPCH deficiency, but these are neither sensitive nor specific. DRD due to TH deficiency can be distinguished from DRD due to GTPCH deficiency by measuring cerebrospinal fluid (CSF) catecholamines, their metabolites, and pterins. In practice, diagnosing DRD by its exquisite response to levodopa typically is sufficient. In some cases, a specific diagnosis is required, either for the purpose of genetic counseling or, in atypical cases, warranting CSF investigations or genetic testing.

It is important to recognize the entity of DRD because it responds dramatically to low doses of levodopa. DRD has been misdiagnosed as cerebral palsy, particularly spastic diplegia. Therefore, it is important to develop suspicion for DRD in children who have motor impairment, prominent dystonia, and a slowly progressive rather than static course. With appropriate diagnosis and treatment, affected children can lead normal lives.

Idiopathic Generalized Torsion Dystonia (*DYT1*)

Childhood-onset idiopathic torsion dystonia, formerly known as dystonia musculorum deformans, is an autosomal dominant condition with incomplete (30%) penetrance. Genetic studies have found that a GAG deletion at the *DYT1* locus on chromosome 9 causes most cases of autosomal dominant, early-onset, primary generalized dystonia affecting Ashkenazi Jewish families (90%) and non-Jews (50% to 60%). In childhood-onset idiopathic torsion dystonia, symptoms usually begin in a limb at a mean age of 12.5 years. Onset typically is before 28 years of age but seldom before age 6 years. The legs generally are affected before the arms, and symptoms usually become generalized within 5 years. Diagnosis is based on identifying a GAG deletion in the *DYT1* gene; genetic testing is available commercially.

Treatment

Treatment of most types of dystonia can be difficult, and often the response is incomplete. The clear exception is DRD, which responds dramatically to low doses of levodopa. For this reason, a trial of levodopa with carbidopa is recommended for all children who have primary dystonia. Because some secondary dystonias also may respond to levodopa, a trial of levodopa is recommended for any child in whom dystonia is a prominent component of his or her neurologic syndrome. The anticholinergic medication trihexyphenidyl has been used with success in some patients who have dystonia. Some patients who were believed to have idiopathic torsion dystonia and had a dramatic response to anticholinergic medication have been shown to have DRD due to GTPCH deficiency. Thus, dramatic response to trihexyphenidyl should suggest the possibility of DRD.

If benefit is inadequate from levodopa or trihexyphenidyl, baclofen alone or in combination with trihexyphenidyl may be beneficial. Intrathecal baclofen has been found to be effective in treating dystonia due to cerebral palsy, but adverse effects are frequent and can be serious. For that reason, we recommend an adequate trial of oral baclofen before considering intrathecal baclofen. Benzodiazepines also may be beneficial, but often the benefit is limited by adverse effects or tolerance.

If oral medications are ineffective, botulinum toxin injections may be highly effective, especially if impairment or disability is attributable to a few muscle groups. Deep brain stimulation of the medial globus pallidus has been used with increasing success for a select group of patients who have dystonia and may be the most effective treatment for dystonia due to the *DYT1* mutation. Because of the broad differential diagnosis of dystonia and the complexities of treatment, we recommend that any patient who has dystonia be evaluated by a neurologist.

Myoclonus

Myoclonus is characterized by brief, abrupt, involuntary, nonsuppressible, jerky contractions involving a single muscle or muscle group. The rapidity of the movements warrants the descriptor "shocklike" or "lightning-fast," as if an electrical shock had just been applied to the peripheral nerve innervating the muscle. Myoclonus can be rhythmic, in which case it often appears tremor-like. However, in true tremor, the movement oscillates with near-equal amplitude around a midpoint; in myoclonus, the movement has a more "sawtooth" character. In some cases, myoclonus can be elicited by a sensory stimulus (reflex myoclonus, with the most famous example being the acoustic startle response in infancy) or volitional movement (action myoclonus). Myoclonus can be focal, multifocal, segmental, or generalized. Occasional myoclonus is seen as a sudden muscle relaxation rather than active contraction. In the case of sudden relaxation causing a visible jerk, the term "negative myoclonus" has been used. (For an example of a baby who demonstrates myoclonus, view the fifth segment of the video in the data supplement.)

The causes of myoclonus are numerous. A first step in

classifying myoclonic disorders is to determine if the myoclonus is epileptic. Electroencephalography is the most useful tool in making this distinction. Myoclonus can be the manifestation of epileptic neurodegenerative diseases such as progressive myoclonic epilepsy, Lafora body disease, and neuronal ceroid lipofuscinosis, as well as mitochondrial diseases such as myoclonic epilepsy and ragged-red fiber disease (MERRF). A full discussion of epileptic myoclonus is beyond the scope of this review.

Important causes of nonepileptic myoclonus are listed in Table 5. The location and quality of myoclonic movements can be helpful in determining cause. For example, segmental myoclonus of thoracic muscles suggests spinal cord pathology, whereas segmental myoclonus of palatal muscles suggests a brainstem lesion or Whipple disease. Asterixis, a form of negative myoclonus, suggests metabolic encephalopathy. Myoclonus in the setting of opsoclonus or ataxia suggests paraneoplastic syndrome (eg, neuroblastoma) or a peri-infectious autoimmune process. Alternatively, myoclonus can be a manifestation of neurodegenerative processes such as lysosomal storage diseases, Wilson disease, or Huntington disease. Diffuse central nervous system injury from virtually any cause (toxic, infectious, metabolic, hypoxic) can result in myoclonus. Essential myoclonus (ie, myoclonus of undetermined cause) typically is a diagnosis of exclusion. Myoclonus, even nonepileptic forms, may respond to anticonvulsant medications such as valproate, levetiracetam, or clonazepam. Given the complex differential diagnosis associated with myoclonus, we recommend that any affected pediatric patient be evaluated by a pediatric neurologist.

Table 5. Causes of Nonepileptic Myoclonus

Physiologic
• Hiccups
• Hypnic jerks (sleep starts)
• Nocturnal myoclonus
Essential
Developmental
Psychogenic
Symptomatic
• Storage diseases
• Basal ganglia degenerations
• Dementias
• Infections
• Metabolic conditions
• Toxic
• Hypoxia
• Focal damage

Tremor

Tremor is a rhythmic oscillation about a central point or position involving one or more body parts. Tremor in childhood is not rare, but few epidemiologic data are available to indicate the incidence or prevalence. Tremor is classified by when it occurs: with rest, intention, or action. Rest tremor is defined as tremor involving a body part that is inactive and supported against gravity. Rest tremor is associated most commonly with other signs of parkinsonism but may occur in isolation. In children, the most common cause of rest tremor is antipsychotic (neuroleptic) medications. Intention tremor occurs as a moving body part approaches a target. Intention tremor usually is associated with other signs of cerebellar dysfunction. Action tremor occurs during maintained posture, voluntary movement, or both. In evaluating the child who has tremor, attention should be paid to possible other neurologic signs or symptoms. When present, such features usually direct the diagnostic evaluation. When tremor is the only abnormality, it is important to identify potential tremor-enhancing medications. The primary laboratory tests to be considered are thyroid function tests.

The most important childhood tremors are action tremors and include physiologic tremor and essential (familial) tremor. Physiologic tremor is a normal phenomenon, consisting of a 6 to 12-Hz oscillation that usually is noticed by the individual or other observers only under certain conditions. A few individuals have a more easily noticed physiologic tremor that is termed "enhanced physiologic tremor." Such individuals otherwise are indistinguishable from those who have no enhanced physiologic tremor. Physiologic tremor may increase with anxiety, excitement, fear, or certain medications. These medications include sodium valproate, theophylline, beta-agonists, corticosteroids, and stimulants. The tremor of hyperthyroidism is an enhanced physiologic tremor.

Essential tremor often is considered a disorder of adults but can begin in infancy or childhood. Essential tremor is the most common movement disorder in adults, but it appears to be less common in children. Essential tremor is present with posture and with action but usually is greatest with maintained posture. The tremor typically involves the upper extremities but may involve the head and neck, voice, and legs. By definition, essential tremor is unaccompanied by other neurologic abnormalities, although individuals

may have slight clumsiness. Essential tremor is "familial" (autosomal dominant) in about 60% of cases. There have been no studies of treating essential tremor in children, but experience has shown that children respond to the same medications that are effective in adults. The most effective medications are propranolol (or other beta blockers) and primidone. Clonazepam may be effective in some cases. Children should be referred to a neurologist for diagnosis and treatment of essential tremor.

Drug-induced Movement Disorders

The phenomenologic classification of drug-induced movement disorders is the same as for nondrug-induced disorders. However, because medications are a relatively common cause of movement disorders in children, they deserve special consideration. Perhaps the best known drug-induced movement disorders are those associated with antipsychotic (neuroleptic) treatment. These medications are dopamine receptor antagonists and cause both acute and tardive (ie, "late") syndromes. The acute adverse effects of dopamine antagonists include parkinsonism and acute dystonic reactions. Acute dystonic reactions can occur even after a single dose of a dopamine antagonist. The typical acute dystonic reaction involves involuntary gaze deviation (oculogyric crisis), torticollis, and appendicular twisting postures associated with axial more than appendicular muscles. The reaction can last for hours but is readily treated with anticholinergic medications such as diphenhydramine (1 mg/kg per dose every 6 hours) or benztropine (0.5 to 2 mg daily or twice a day).

The most severe reaction to dopamine antagonists is the neuroleptic malignant syndrome (NMS), which is characterized by hyperthermia, hypertonia, dystonic posturing, tremor, and autonomic instability. NMS can be fatal. Children suspected of having NMS should be evaluated promptly by a neurologist. Treatment primarily is supportive and consists of controlling fever and correcting metabolic abnormalities. Dantrolene should be given to diminish excessive muscle contraction. Dopamine agonists such as bromocriptine may be effective. Neuroleptic medications should be discontinued.

Tardive dyskinesia (TD) is uncommon in childhood. The dyskinesia can manifest as any of the hyperkinetic movement disorders. TD typically manifests as an oro-buccal-lingual stereotypy, but it can involve other body parts. The risk of TD increases with total dose and treatment duration of antipsychotic medication and with age of the patient. There is some evidence that children who have suffered previous brain injuries are more likely to develop TD.

Extrapyramidal effects such as acute dystonic reaction, parkinsonism, and TD are substantially more likely to occur with the older, so-called "typical" neuroleptic medications such as haloperidol and pimozide and other dopamine-blocking agents such as metoclopramide and prochlorperazine. Atypical neuroleptic medications, such as risperidone, quetiapine, olanzapine, and ziprasidone, have a demonstrably lower incidence of such extrapyramidal effects, but such adverse effects can occur. Treatment of TD can be difficult and requires referral to a neurologist or psychiatrist experienced in its treatment. Prevention of TD requires care in avoiding indiscriminate use of antipsychotic medications, limiting duration of treatment, and minimizing total daily dose.

Many other medications have been associated with movement disorders. The more common ones are summarized in Table 6. The treatment of drug-induced movement disorders is to eliminate the offending agent whenever possible. In most cases, it does not make sense

Table 6. Common Drug-induced Movement Disorders

Medications*	Reaction
Dopamine antagonists (antipsychotics) • Haloperidol • Pimozide • Chlorpromazine • Metoclopramide • Prochlorperazine • Risperidone	Acute dystonic reaction Tardive dyskinesia Withdrawal dyskinesia Parkinsonism Neuroleptic malignant syndrome
Antiepileptic agents • Phenytoin • Carbamazepine • Sodium valproate	Chorea Dystonia Tremor
Beta-adrenergic agonists • Albuterol • Metaproterenol	Tremor
Amphetamines	Chorea Tremor
Cocaine	Chorea
Lithium	Chorea Tremor

*Common examples are listed, but the list is not intended to be comprehensive.

to administer another medication to treat adverse effects from the drug causing a movement disorder.

Summary

- Movement disorders in children can be complex. Identification of the specific type of abnormal movement based on the spatial–temporal features is the essential first step toward diagnosis.
- Specific diagnosis of these disorders usually requires evaluation and treatment by a neurologist.
- In most cases, treatment is symptomatic and depends on the specific movement disorder.
- Most treatment recommendations for the pediatric movement disorders discussed in this review are based on expert consensus and extrapolation from studies in adults who have comparable movement disorders.

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PIR Quiz

Quiz also available online at http://pedsinreview.aappublications.org.

9. You are evaluating a 10-year-old girl who had a group A beta-hemolytic streptococcal infection 1 month ago. Among the following, the finding *most* consistent with a diagnosis of Sydenham chorea is:

   A. Asymmetric chaotic-appearing involuntary movements.
   B. Catatonia.
   C. Diminished deep tendon reflexes.
   D. Hypertonia and dysphagia.
   E. Muscle fasciculations

10. You are asked to evaluate a 12-year-old boy who has an acute dystonic reaction. He has a longstanding history of gastroesophageal reflux disease. Among the following, the drug *most* likely to cause his dystonia is:

    A. Aluminum-magnesium hydroxide.
    B. Famotidine.
    C. Metoclopramide.
    D. Omeprazole.
    E. Sucralfate.

11. A father brings his 9-year-old son to your clinic for evaluation of a bilateral tremor. The child has a history of epilepsy. Among the following, the drug *most* likely to be responsible for the tremor is:

    A. Carbamazepine.
    B. Clonazepam.
    C. Levetiracetam.
    D. Primidone.
    E. Valproate.

12. A mother brings her 16-year-old daughter to you because every morning upon waking the girl unexpectedly tosses her toothbrush or a teacup. You worry that these shocklike movements represent myoclonus. Of the following, the *most* appropriate first step to evaluate this girl is:

    A. Antistreptolysin O titer.
    B. Electroencephalography.
    C. Psychiatry consultation.
    D. Serum lactate measurement.
    E. Urine toxicology screen.

13. A mother brings her 13-year-old son to your clinic because he refuses to handwrite his high school assignments, insisting upon using a computer. He complains that his hand goes into a twisted, abnormal posture when he writes. There are no abnormal movements in other parts of his body. Among the following, the *most* likely diagnosis is:

    A. Attention-deficit/hyperactivity disorder.
    B. Dopa-responsive dystonia.
    C. Learning disability.
    D. Physiologic tremor.
    E. Writer's cramp.

Movement Disorders II: Chorea, Dystonia, Myoclonus, and Tremor

Jonathan W. Mink and Samuel H. Zinner

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Research and Statistics: Strengths and Limitations of Randomized, Controlled Trials

Erica M.S. Sibinga and Jacky M. Jennings

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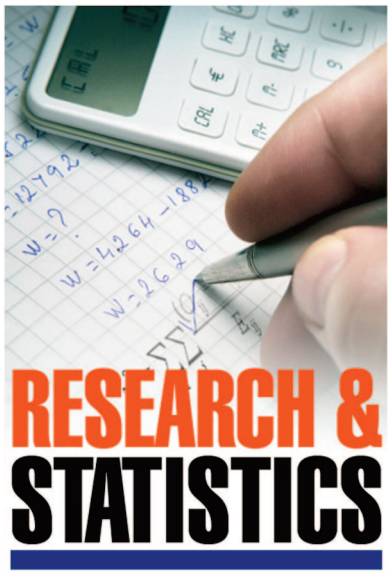

Author Disclosure

Drs Sibinga and Jennings have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Strengths and Limitations of Randomized, Controlled Trials

Erica M.S. Sibinga, MD, MHS,* Jacky M. Jennings, PhD, MPH*

Case Study

The father of a 3-year-old boy, who has just started preschool, brings the boy to your office for "his fourth cold in a row." The boy was back to his baseline last week but now has congestion and rhinorrhea. On physical examination, he is afebrile and has no signs of otitis media or lower respiratory tract involvement. His father expresses frustration with these frequent illnesses and asks if there is something else he can do. As a general pediatrician, you often are confronted with this clinical scenario. You recall a recent study of probiotics for the prevention of colds and influenza-like illnesses and review it more carefully.

Leyer and associates (1) conducted a prospective, randomized, double-blind, placebo-controlled study of 326 children, in which 3- to 5-year-old children received one of three products for 6 months. Probiotic I consisted of one strain of probiotic, probiotic II consisted of two strains of probiotic, and a placebo preparation contained no probiotics. The investigators found that compared with placebo, both probiotic groups had reductions in fever, coughing, rhinorrhea, antibiotic use, and missed school days due to illness. You are excited to tell this frustrated father about probiotics but pause to reflect on how best to apply the results of this study specifically to his son.

Randomized, Controlled Trials

Randomized, controlled trials (RCTs) are considered the "gold standard" among research designs, and their results are widely viewed as the strongest form of research evidence. The strength of this study design comes from: 1) the study participants being *randomly* assigned to the study condition (experimental or control) and 2) a control arm being present, against which to compare the effects seen in the experimental arm. RCTs are used most often to compare new treatments or approaches (in this case, probiotics) with current treatment (in this case, approximated by placebo). In an RCT, the study population is carefully determined before beginning the study (in this case, healthy children 3 to 5 years of age in a child care center in China), study participants are assigned randomly to either the experimental group(s) or the control group (probiotic I, probiotic II, or placebo), and participants receive either the experimental or control treatment according to group assignment during the study period.

Unlike other study designs, participants from a single subject pool are assigned randomly to their study condition, which should lead to a balance of baseline confounders (known and unknown subject differences relevant to the outcome of interest) across the experimental and control arms. If randomization is successful and the groups are balanced at baseline, the researcher can conclude that differences between the experimental and control groups at the end of the study are due to the experimental treatment itself. In the case of the Leyer study, the randomization was not entirely balanced; the placebo group had an older average age, which may have been the result

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of the modest sample size. To account for the age imbalance between groups at baseline, age was adjusted for in subsequent analyses. Such issues highlight the complexity of conducting RCTs, despite high levels of rigor. Compared with other study designs, RCTs tend to be more time-consuming and expensive.

Interpreting Results

Despite the strengths of the RCT design, a few important considerations should be kept in mind when interpreting results from or designing RCTs. First, not all research questions can be answered with an RCT. For example, recruiting participants for an RCT may not be possible when studying very personal choices (eg, breastfeeding, corporal punishment, educational choices). Further, unless both study arms are understood to be clinically equivalent (state of equipoise), it may not be ethical to randomize treatments. (2)

Another important factor is how the study population compares with the general population or with a particular population of interest. It is important to consider how restrictive the eligibility criteria are, how the study procedures themselves might exert a bias (are the study conditions unusually burdensome?), and how participants move through the study (eg, rates of dropout, nonadherence). For example, the probiotics study was conducted in China, and it is important to consider if the location introduced relevant systematic biases.

Finally, what element of the intervention is controlled for by the control group? Ideally, the control group experiences what are believed to be the nonspecific aspects of the intervention (eg, the benefits of getting a placebo), and the experimental group experiences the nonspecific (eg, the benefits of the placebo) plus the specific aspects (the benefits of the active ingredient). If the control group effectively controls for the nonspecific effects, differences between groups can be attributed to the specific effect.

In an attempt to improve the transparency related to the reporting and interpretation of RCTs, the CONSORT (Consolidated Standards of Reporting Trials) statement now is used widely to guide the publication of RCTs. (3)(4) The central issues addressed by the CONSORT guidelines include the requirement for clear descriptions of: the study population (inclusion and exclusion criteria), participant flow (a diagram tracking all participants is suggested), group treatment (for experimental and control groups), randomization procedures, blinding (participants, those administering intervention/control, those collecting data, data analysts), primary and secondary outcomes, and numbers analyzed. As seen in the Leyer study, the broad use of the CONSORT guidelines can facilitate readers' ability to interpret RCT results appropriately for their needs.

Conclusion

After careful consideration of the Leyer study with these issues in mind, you feel comfortable assessing the strengths and weaknesses of RCT and discussing the use of probiotics for the prevention of upper respiratory tract symptoms with this father.

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Research and Statistics: Strengths and Limitations of Randomized, Controlled Trials

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Visual Diagnosis: A Pimple-like Lesion on the Cheek of a 5-year-old Girl

Rayna M. Dyck and Dawn M. Davis

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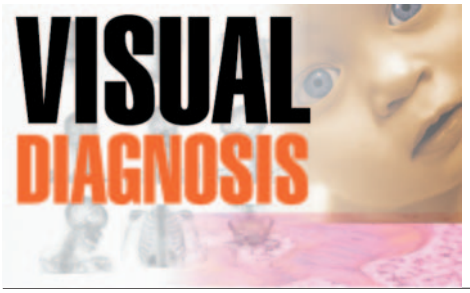

A Pimple-like Lesion on the Cheek of a 5-year-old Girl

Rayna M. Dyck,* Dawn M. Davis, MD†

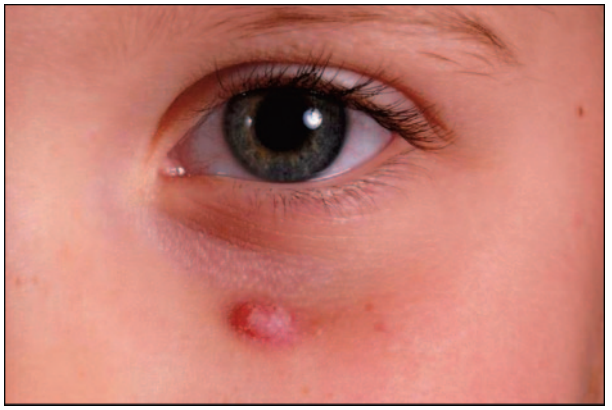

Figure 1. Clinical presentation of 6-mm pimple-like lesion below the left eye.

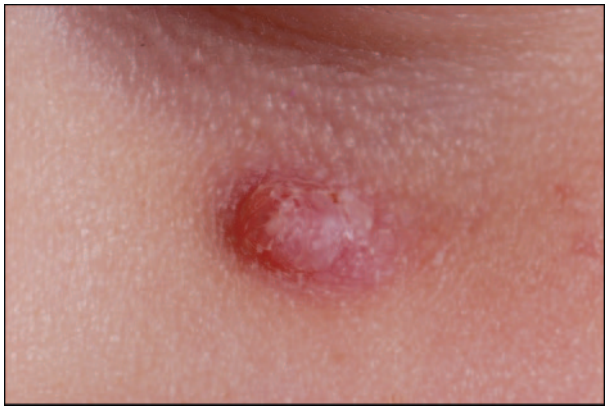

Figure 2. Closer view of the raised, erythematous lesion.

Author Disclosure

Ms Dyck and Dr Davis have disclosed no financial relationships relevant to this case. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Presentation

A healthy-appearing 5-year-old girl comes to the dermatology clinic for evaluation of a lesion on her face that has been present for at least 3 years. The lesion started as a pimple-like growth on her left superior cheek near the lower eyelid, subsequently grew in size, but has been stable in size for the past 1 to 2 years. The lesion is only occasionally tender when bumped, but the patient and parents report no precipitating trauma to the area. The lesion previously was believed to be a wart and was treated with imiquimod (a topical immune response modifier used to treat superficial basal cell carcinoma, actinic keratosis, and external genital and perianal warts), but no significant change was seen after approximately 2 weeks of use. Later, a primary care physician applied liquid nitrogen cryotherapy to the lesion, resulting in only some superficial sloughing. The patient was seen by another dermatologist, who again prescribed imiquimod for the presumed wart, but the parents chose to get another opinion.

The patient's past medical and surgical history includes prior eustachian tube dysfunction requiring pressure-equalization tubes and a severe reaction to chickenpox requiring hospitalization. Her perinatal history is unremarkable. She is taking no medications.

On physical examination, the lesion is a 6-mm, raised, erythematous papule that is semifirm to palpation (Figs. 1 and 2). No underlying dermal component is appreciated; under epiluminescence microscopy (also known as dermoscopy), the lesion appears to have prominent vascularity. No other lesions are noted on the face, neck, and scalp.

Because of the location of the lesion on the face, the patient is referred to the plastic surgery department for removal. The lesion is excised, and on the basis of pathologic findings, a diagnosis is suspected.

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Diagnosis: Malignant Melanoma (Spitzoid and Nodular Type)

Histopathologic analysis showed a malignant melanoma without ulceration, spitzoid type, and nodular type (Figs. 3 and 4). The tumor was Clark level IV and 2.6 mm in Breslow thickness (T classification: T3a). Immunohistochemical studies showed tumor cells that were S-100 positive and weakly Melan-A-positive. An HMB-45 immunostain highlighted focal deep nodules of tumor cells, and an MIB-1 immunostain highlighted increased proliferative activity throughout the dermis within the tumor cells. S-100 normally is found in cells derived from the neural crest, such as melanocytes. HMB-45 is a monoclonal antibody against an antigen present in melanocytic tumors. S-100 is highly sensitive for melanomas, and HMB-45 is highly specific for these tumors. Melan-A (also known as MART-1) is a protein antigen found on melanocytes, and although it is a useful marker for melanocytic tumors, it also can be found in benign nevi.

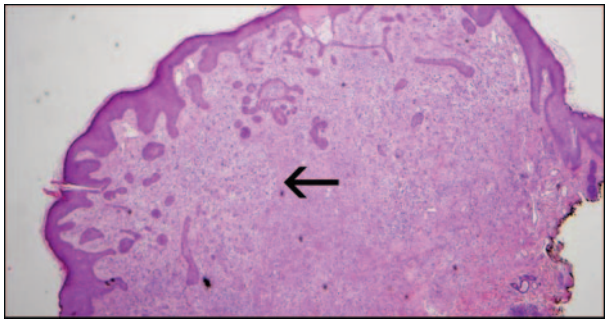

Figure 3. Histopathologic sample of the lesion (hematoxylin-eosin, original magnification ×4), showing atypical melanocytic nests.

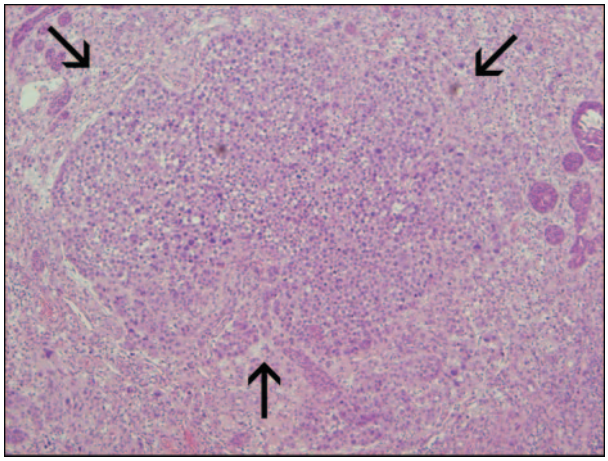

Figure 4. Histopathologic sample of the lesion (hematoxylin-eosin, original magnification ×4), showing atypical melanocytic nests. Arrows point to blue-elled nodule, which is a nodular focus of the melanoma.

The tumor also was found to involve the lateral inked margins of the biopsy specimen. Therefore, a complete re-excision of the lesion with clinically appropriate margins was recommended. Subsequently, the patient underwent whole body positron emission tomography, which showed no evidence of metastases. A wide local re-excision was performed as well as a sentinel lymph node biopsy. Pathologic and immunohistochemical analysis showed no residual melanoma and documented the sentinel node to be negative for Melan-A, S-100 protein, and tyrosinase. Additional biopsies showed multiple lymph nodes to be negative for tumor.

Discussion

The American Cancer Society reports that 59,940 new cases of melanoma were reported in 2007, along with 8,110 deaths attributable to the disease. The Centers for Disease Control and Prevention estimated the occurrence of 506 new cases of melanoma in the United States in 2004 in persons ages 19 years and younger and 55 new cases in children younger than 10 years of age (1). Although pediatric melanoma may be rare, its incidence has been reported to be increasing. In the United States, the incidence of pediatric melanoma increased 46% per year of age and 2.9% per year from 1973 to 2001. (2)

As in adult melanoma, most pediatric melanomas are cutaneous, but they present differently in the pediatric population. In 2005, one study showed that compared with adult melanoma, pediatric melanomas have a higher frequency of atypical features, thicker lesions at diagnosis, a higher proportion of the nodular histotype, and a higher frequency of developing in particular sites. (3) In children, as opposed to adults, there is a disproportionate number of amelanocytic melanomas. Many childhood melanomas have features of both nodular and amelanocytic melanomas. Many melanomas in children are misdiagnosed as pyogenic granulomas.

Risk factors for pediatric melanoma include white race, female sex, increasing age, and environmental ultraviolet (UV) exposure. Because the only modifiable risk factor is UV exposure, it is important to educate parents and younger patients about the importance of sun protection very early in life. Case-control studies of adults have shown that increased UV exposure (ie, blistering sunburns) confers a two- to fivefold increased risk of melanoma.

Pediatric melanoma is difficult to diagnose, and diag-

nostic concordance is variable, even among dermatopathologists. In this case of a patient who has a nodular melanoma, the differential diagnosis could include pigmented lesions such as the common nevus, blue nevus, pigmented Spitz nevus, and pigmented basal cell carcinoma. The differential diagnosis also includes amelanotic lesions such as basal cell carcinoma, hemangioma, pyogenic granuloma, and Merkel cell carcinoma. If the diagnosis is questionable, a biopsy must be obtained.

When diagnosing pediatric melanoma, clinicians should evaluate the lesion, employing the commonly used ABCDE (asymmetry, border, color, diameter, and evolution) criteria, just as in the adult population. Key features are asymmetry of the lesion, irregularity of its borders, and irregular distribution of color (or pigmentation) within the lesion. The size of the lesion also is important. Although Spitz and other benign nevi tend to be regular-appearing and less than 1 cm in diameter, melanomas tend to be larger and less uniform in clinical appearance. It should be noted, however, that many melanomas may be small, so if other clinical characteristics of the lesion are of concern, melanoma should stay in the differential diagnosis. The final key features are changes to any long-standing lesion. These changes could include an increase in size, a change in color or in distribution of color, bleeding, inflammation, swelling, or ulceration. When evaluating a suspicious lesion, clinicians always should palpate for underlying masses and examine for regional lymphadenopathy.

Existing studies of pediatric melanoma have been few. Currently, the diagnosis and treatment of these tumors is the same as for adults. Surgery continues to be the mainstay of initial treatment, with sentinel lymph node biopsy for lesions thicker than 1 mm. Positive sentinel lymph nodes are found more often in patients younger than 35 years of age, and that finding supports the recommendation that sentinel lymph node biopsy be performed in patients in this age group, even if the tumor is less than 1 mm thick. Sentinel lymph node biopsy is performed for purposes of prognostication; the procedure does not seem to offer any survival benefit, and it remains a controversial technique. Adjuvant therapy commonly is not used for those who have localized invasive or only regionally metastatic melanoma. The chemotherapeutic agents used to treat melanoma include dacarbazine, cisplatin, vinblastine, carmustine, interferon alpha, and tamoxifen. Chemotherapy rarely, if ever, results in a cure. Therefore, the best help for patients is prevention, early detection, and removal at an early stage.

Patient Course

The patient has fared well since excision of the melanoma, with no recurrence. A genetics evaluation determined that although the family history is notable for a melanoma in her paternal grandfather and Burkitt lymphoma in her father, her tumor most likely was sporadic. She is being followed by the departments of dermatology and pediatric hematology/oncology via serial positron emission tomography scans.

Summary

- **Although melanoma is rare in the pediatric population and its diagnosis remains difficult, the possibility of this tumor cannot be ignored. Clinicians treating pediatric patients must recognize when a skin lesion warrants biopsy instead of simply considering the questionable lesion to be refractory to treatment and deferring additional investigation.**
- **Future studies must address whether a more specialized diagnostic and treatment approach to melanoma is necessary in the pediatric population.**
- **As in the adult population, early diagnosis is key, with the overall 5-year observed survival being strongly associated with initial summary stage.**

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Visual Diagnosis: A Pimple-like Lesion on the Cheek of a 5-year-old Girl

Rayna M. Dyck and Dawn M. Davis

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Pediatrics in the Community: A Little PUSH to Get the Advocacy Snowball Rolling

Katherine R. Snyder

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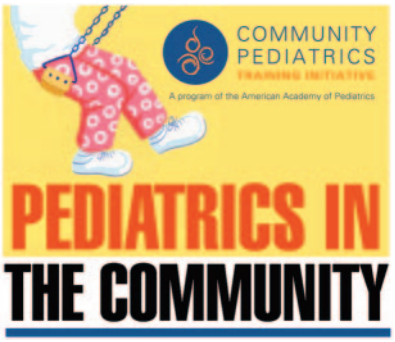

Author Disclosure
Drs Snyder and Aligne have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A Little PUSH to Get the Advocacy Snowball Rolling

Pediatricians Urging Safety & Health (PUSH) is an advocacy group created in 2006 by Dr Josh Honaker, a former resident in pediatrics at the University of Louisville (http://pushkentucky.org/home). Among its successes, PUSH has helped to pass the Graduated Driver License Bill, Booster Seat Bill, and Shaken Baby Bill in the state legislature while also working at a community level. PUSH has sparked interest in advocacy among residents, faculty, and the community. Phone calls or emails are common from these groups for information on topics, state law, or how to be an advocate and start their own projects.

Two thirds of Louisville's pediatric residents participate in this elective activity. Currently, PUSH is focusing on child abuse and obesity, although the specific topics highlighted at any given time are not as important as the underlying process of engaging residents in child advocacy. The energy and excitement of the group has instigated multiple projects outside of the focus areas. For example, one recent resident who was interested in smoking cessation submitted an application for an American Academy of Pediatrics (AAP) CATCH grant. Although he did not get the grant, he obtained a better prize—the experience of the process. He was forced to think through the intricacies of the project and realize that there was more work to do before this project could come to fruition. Months later, together with another resident, he presented an improved plan to the Chairman of the Department of Pediatrics and the PUSH leadership committee, who stayed late after the meeting, energized about the possibly far-reaching impact of the project. This resident went from being not so active to being a dynamo in 1 year's time after the encouragement from peers and advisors.

Every residency class, at its inception, has that handful of people who are natural champions for a cause. Focusing on the development and success of those people creates momentum, which brings others into the group naturally. They see the successes of other residents and start to believe that they can make a difference, too. Once residents are involved, they can't stop.

We all entered pediatrics to make a difference for children and their families: to advocate for them. We do it every day at an individual level in the clinic or hospital. Once residents realize that they can have a more global effect, they start to pay attention to hospital committees as well as to local and national legislative agendas and begin to develop their own project ideas.

Residents administer PUSH with support from the Kentucky Chapter of the AAP, faculty advisors, the program director, the department chair and staff, and several community-based organizations. Each new class re-evaluates organizational structure and priorities and makes any necessary changes. A mission statement keeps them focused and centered on their goal of improving the health and safety of Kentucky's children. PUSH's model follows that of the Olympics: "It's not the triumph, but the struggle." The "struggle" is the goal. This is how we teach; this is how we learn. (*Katherine R. Snyder, MD, MPH, University of Louisville, Louisville, Ky.*)

SECTION EDITOR'S NOTE: One of the difficulties in implementing the AAP policy to train residents in community health and advocacy is the lack of experienced faculty in this area. The PUSH experience indicates that creating an encouraging environment for residency advocacy projects can start a positive feedback loop of seeing, doing, and teaching.—*C. Andrew Aligne, MD*

Pediatrics in the Community: A Little PUSH to Get the Advocacy Snowball Rolling

Katherine R. Snyder

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Index of Suspicion

Scott M. Pugh, Joseph F. Pasternak, Patricia A. Liszewski, Alexandra N. Menchise, Leslie Carroll, David M. Berman, Gurpreet Vidwan and Winsley Rose

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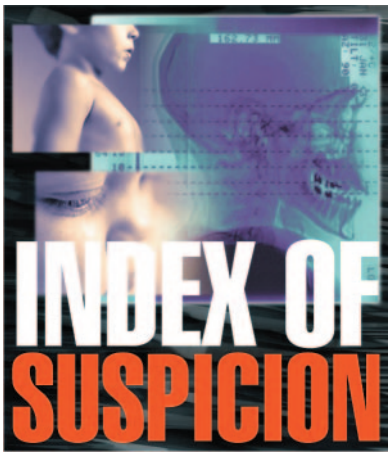

The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting **Dr. Deepak Kamat at dkamat@med.wayne.edu.**

Author Disclosure

Drs Pugh, Pasternak, Liszewski, Menchise, Carroll, Berman, Vidwan, and Rose have disclosed no financial relationships relevant to these cases. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Frequently Used Abbreviations

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CBC:	complete blood count
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
ECG:	electrocardiography
ED:	emergency department
EEG:	electroencephalography
ESR:	erythrocyte sedimentation rate
GI:	gastrointestinal
GU:	genitourinary
Hct:	hematocrit
Hgb:	hemoglobin
MRI:	magnetic resonance imaging
WBC:	white blood cell

Case 1 Presentation

A 10-year-old girl presents with left eye pain 1 day after being hit in the face with a palm tree leaf that sprang back at her while playing. She immediately complained of eye pain, tearing, and blurry vision following the incident. Her pain is improving today, but the tearing and blurred vision remain, and the eye still looks red. She has no fever or headache, and she does not wear glasses or contact lenses. Her past medical history is unremarkable.

Physical examination reveals a well-appearing girl in no acute distress, who prefers to keep her left eye closed. Vital signs are normal and visual acuity is 20/15 in the right eye and 20/200 in the left eye. She has no signs of head or facial trauma. She has moderate photophobia, increased tear production, and significant conjunctival injection in the left eye. Extraocular movements are normal. There is no anisocoria, subconjunctival hemorrhage, or chemosis. Fluorescein is placed in the left eye, and examination under a Woods lamp does not reveal any obvious uptake of dye on the cornea or conjunctiva. The child is taken for urgent consultation with the ophthalmologist, who makes the diagnosis.

Case 2 Presentation

A 2½-year-old girl presents to a community hospital with fever and a limp. Her blood culture grows methicillin-resistant *Staphylococcus aureus* (MRSA), and she is treated empirically with 3 days of intravenous (IV) clindamycin but remains febrile. She is transferred for additional management. Significant findings on her past medical history include a MRSA skin abscess on the left knee treated 3 months ago with trimethoprim-sulfamethoxazole, speech delay, pneumonia, and asthma.

The fair-skinned girl weighs 12.5 kg (25th to 50th percentile), has a temperature of 37.5°C, and has other vital signs within normal range for age. She has blonde hair and bluish-gray eyes. There is full passive range of motion of her extremities. Her gait is abnormal. She favors her right leg, with her left foot externally rotated and left hip abducted. There is no erythema or tenderness in any extremity. The remaining physical findings are normal.

The MRSA-positive blood culture from the transferring hospital shows resistance to clindamycin and susceptibility to vancomycin, rifampin, and trimethoprim-sulfamethoxazole. Her antibiotics are changed to IV vancomycin and rifampin. Her initial CBC shows a WBC count of 6.8×10^3/mcL (6.8×10^9/L), with 10% neutrophils, 77% lymphocytes, and 13% monocytes; Hgb of 9.9 g/dL (99 g/L); Hct of 31.1% (0.311); mean corpuscular volume of 67.2 fL; mean corpuscular hemoglobin of 21.4 pg; and platelet count of 232×10^3/mcL (232×10^9/L). Comprehensive metabolic panel results are unremarkable. C-reactive protein measures 2.5 mg/dL. Repeat blood culture shows no growth. MRI and radiograph of the femur show normal results. Spine MRI shows evidence of osteomyelitis involving the left S1 segment of the sacrum.

Case 3 Presentation

A 12-year-old girl is admitted to the hospital after her first seizure. Her friends noticed that she "passed out" on the school bus the morning of admission and then experienced 2 minutes of both arm and leg jerking movements. She was unresponsive and had urinary incontinence during the episode. The movements resolved spontaneously, and she was acting normally by the time paramedics arrived to transport her to the hospital. She had

been complaining of intermittent headache for 1 week before the seizure. She denies fever, visual changes, vomiting, recent illness, or recent travel. She is not taking any medicines. Her parents emigrated from Guatemala, and her father works as a farm laborer.

On physical examination, the girl is alert, oriented, and in no apparent distress. Her vital signs are normal. She has completely normal neurologic and musculoskeletal examination findings. Her complete metabolic profile, CBC, urinalysis, urine drug screen, and C-reactive protein value are normal. Her clinical history and imaging studies lead to the diagnosis.

Case 1 Discussion

This child easily could have had a healing corneal abrasion diagnosed and been sent home. However, her significantly impaired visual acuity despite improvement in pain combined with the absence of fluorescein uptake was concerning for a more serious ocular injury. A central corneal abrasion might account for some decreased visual acuity, but improvement would be expected after 24 hours. Under slitlamp examination by the ophthalmologist, the anterior chamber of the left eye appeared shallow (Fig. 1) and a leak was evident through a perforated cornea (Fig. 2). Handheld penlight examination did not demonstrate these features.

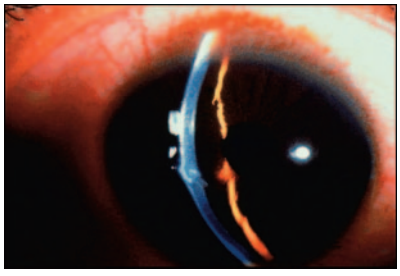

Figure 1. Shallow anterior chamber from central perforation of the cornea.

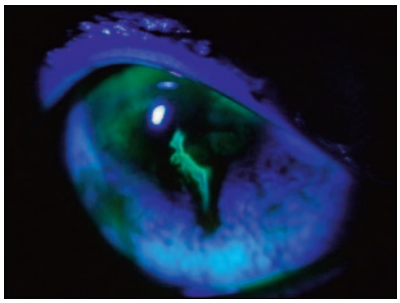

Figure 2. Egress of aqueous humor through full-thickness traumatic laceration.

Initial attempts to seal the leak with a bandage contact lens and pressure patch did not succeed. Eventually, the girl required sedation and suturing of the cornea as an ambulatory procedure. She also received topical fluoroquinolone and oral ciprofloxacin for 72 hours. One day after closure, the anterior chamber had reformed, and she showed no signs of intraocular infection. The suture was removed after 2 weeks, and her vision returned to 20/20 in the affected eye.

The Condition

A ruptured globe is defined as any perforation of the anterior or posterior segment of the eye. Perforation can occur at any location from sharp penetrating objects; blunt force more commonly causes rupture at the limbus or behind the rectus muscle insertions where the sclera is weakest. Signs of globe rupture include subconjunctival hemorrhage, chemosis, pupillary defects, vitreous hemorrhage, or retained foreign bodies and may be associated with visual impairment out of proportion to the injury. As aqueous humor leaks through the defect, it can wash away fluorescein dye, making it difficult to detect the tear. Globe rupture and laceration frequently lead to permanent visual impairment either through direct damage to the eye or through aberrant healing (cellular infiltrate) or infection (endophthalmitis).

Differential Diagnosis

A corneal abrasion is disruption of the epithelial covering that protects the cornea. It is caused frequently by trauma or foreign body but also can result from infection. Patients usually experience immediate severe pain, photophobia, and tearing. Often they experience the sensation of a foreign body. The area of exposed corneal tissue should take up fluorescein dye and be apparent under Woods lamp examination. Care must be taken to rule out a corneal foreign body, ulcer, or infiltrate. The abrasion heals when surrounding tissue regenerates the epithelial defect, a process that typically requires a few days, depending on the size of the initial wound.

Management

If a globe rupture is suspected, the examination should stop and a simple protective eye shield should be placed. Immediate referral to an ophthalmologist, potentially in a tertiary care center, is critical because surgical closure often is required. It is important to avoid any manipulation (such as patching) that could increase intraocular pressure and possibly cause extrusion of intraocular contents. Broad-spectrum parenteral or oral antibiotics should be administered early in the course to reduce the risk of endophthalmitis, which can have devastating effects.

Simple corneal abrasions (<10 mm) can be treated with topical antibiotics. Occasionally, an ophthalmoplegic agent may be used to relieve pain associated with ciliary spasm. A suspected corneal abrasion in a contact lens wearer warrants immediate referral to ophthalmology to rule out a corneal ulcer.

Retained foreign bodies in the

scleral or palpebral conjunctiva often can be removed in the primary care setting. After instilling the topical anesthetic, the object may be brushed away by using a cotton-tipped swab. This removal should be followed by copious irrigation and treatment of any underlying corneal abrasion.

Lessons for the Clinician

- Corneal abrasions are common, but when the history or examination results are not consistent with the expected course, globe rupture should be considered.
- Visual acuity testing is an important part of the physical examination that must not be overlooked when patients have perceived visual impairment or other eye complaints.
- Early closure and prevention of endophthalmitis are paramount in preserving vision.

(*Scott M. Pugh, MD, Joseph F. Pasternak, MD, Patricia A. Liszewski, MD, United States Naval Hospital, Naples, Italy*)

The views expressed in this case are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the United States government.

Case 2 Discussion

Based on a peripheral blood smear showing giant cytoplasmic granules within neutrophils (Fig. 3) and hair analysis revealing silver hair without medullary core pigmentation (Fig. 4), Chediak-Higashi syndrome (CHS) was diagnosed.

Immune evaluation included T- and B-lymphocyte enumeration; lymphocyte transformation to antigen and mitogen stimulation; quantitative immunoglobulins; and anti-diphtheria, anti-tetanus, and anti-pneumococcal antibody titers. Test results were normal. Epstein-Barr virus (EBV) antibody titers revealed past EBV infection. DNA analysis showed CHS-1 mutation, confirming the diagnosis of CHS.

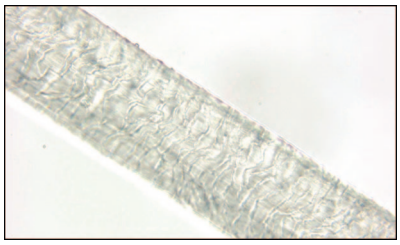

Figure 4. Hair analysis shows silver hair without medullary core pigmentation.

Although anemia can be associated with CHS, this patient's microcytic anemia can be explained by iron deficiency from increased cow milk ingestion. In addition, this girl had neutropenia (absolute neutrophil count of 0.680×10^3/mcL [0.680×10^9/L]), which is a feature of CHS.

Once she improved clinically, her IV antibiotics were discontinued and she was started on oral trimethoprim-sulfamethoxazole. She did well clinically. Subsequently, she underwent a matched unrelated donor bone marrow transplant for her CHS and is doing well at this time.

The Condition

CHS is a rare autosomal recessive disorder, with fewer than 500 cases reported worldwide in the past 20 years. It is characterized by oculocutaneous albinism, recurrent pyogenic infections, progressive neurologic problems, and mild coagulation defects. It presents in infancy or childhood. This patient had oculocutaneous albinism and recurrent pyogenic infections without neurologic insult.

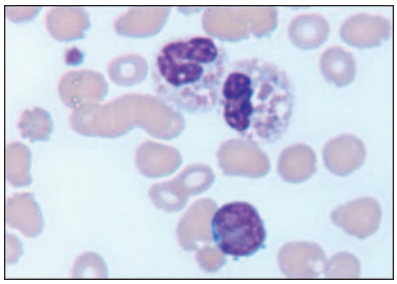

Figure 3. Peripheral blood smear shows giant cytoplasmic granules within neutrophils.

Affected patients usually have fair skin. The hair typically is blonde, gray, or white and has a metallic sheen. The eyes usually are light. Strabismus, photophobia, and progressive visual loss are common. Morbidity and mortality are increased by pyogenic infections, most commonly from *Staphylococcus aureus* and *Streptococcus pyogenes*. Infections include cellulitis, abscesses, superficial pyoderma, periodontal disease, and enterocolitis. The clinical presentation for CNS involvement includes seizures, peripheral neuropathy, weakness, ataxia, tremors, and cognitive decline.

Severe immunodeficiency and massive lymphohistiocytic infiltration of organ systems occurs in most patients. This occurrence is described as the accelerated phase of CHS and is characterized by hepatosplenomegaly, pancytopenia, lymphadenopathy, and bleeding diathesis. It has been hypothesized that the accelerated phase may be an expression of the familial form of hemophagocytic lymphohistiocytosis that may be triggered by viral infections such as EBV.

Pathogenesis

Mutations in the lysosomal trafficking regulator gene (*CHS1/LYS*) are the underlying defect in CHS. These mutations can result in absent or abnormal CHS1/LYST proteins. It is hypothesized that such defective proteins lead to abnormal protein trafficking and fusion of vesicles as well as failure to transport lysosomes to the designated sites of action.

All cell types are affected in CHS. Cytotoxic T cells and neutrophils have abnormal granules that do not

function when exposed to pathogens, resulting in severe infection. In melanocytes, the melanosomes are not transferred to epithelial cells or keratinocytes, resulting in albinism. A reduction in platelet-dense bodies can result in mild coagulation defects.

Diagnosis

Giant azurophilic cytoplasmic granules in granule-containing cells are pathognomonic for CHS. Diagnosis can be confirmed by genetic testing for *CHS1/LYST* gene mutations. Light microscopy of the hair shaft reveals accumulation of irregularly distributed pigmentation that appears bright and polychromatic under polarized light microscopy. The diagnosis can be made prenatally by sampling fetal blood, fetal hair, or amniotic and chorionic villus cells.

Neutropenia and hypergammaglobulinemia, with preserved B-cell function, are common findings. Platelet aggregation and bleeding time can be abnormal. In the accelerated phase of CHS, thrombocytopenia can occur.

Differential Diagnosis

Differential diagnosis for a patient who has oculocutaneous albinism and immunodeficiency includes Griscelli syndrome, a rare autosomal recessive disorder. The lack of intracellular granules within cells and polarized light microscopy examination of the hair shaft revealing a uniformly white appearance distinguishes it from CHS. Hermansky-Pudlak syndrome is another rare autosomal recessive disorder characterized by partial oculocutaneous albinism and platelet storage pool deficiency caused by a different genetic mutation from CHS. Waardenburg syndrome, Prader-Willi syndrome, and Angelman syndrome also should be considered.

Treatment

The gold standard treatment is hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen-matched donor. Transplantation should occur before the accelerated phase or during remission. Successful HSCT improves prognosis, reduces risk of infection, and prevents development of the accelerated phase. HSCT does not prevent neurologic sequelae or albinism. Without transplantation, most patients die from infection in childhood.

As with other immunodeficiency syndromes, prophylactic antimicrobial drugs and aggressive therapy for infection is the mainstay of therapy. Various case reports document success with granulocyte colony-stimulating factor and interferon-gamma in reducing the risk of infection. For patients in the accelerated phase, glucocorticoids, splenectomy, antiviral therapy, chemotherapy, and intravenous gamma globulin have been used with variable success.

Lessons for the Clinician

- Although rare, patients presenting with oculocutaneous albinism and recurrent pyogenic infections should be evaluated for CHS.
- Diagnosis is made by identifying cytoplasmic granules on a peripheral blood smear and genetic mutation testing.
- Infection is the most common cause of mortality.
- Prognosis is poor, even with successful stem cell transplantation, because patients endure debilitating neurologic sequelae in adulthood.
- Medical and social care is provided best by a coordinated team of specialists due to the complexity of this syndrome.

(*Alexandra N. Menchise, MD, Leslie Carroll, MD, David M. Berman, DO, All Children's Hospital, St. Petersburg, Fla.*)

Case 3 Discussion

Brain MRI revealed a solitary 9-mm ring-enhancing lesion in the left superior parietal lobe (Fig. 5). The lesion raised concern primarily for an abscess due to *Mycobacterium tuberculosis*, *Nocardia*, *Actinomyces*, or *Aspergillus* infection or neurocysticercosis (NCC). Other causes for this type of lesion include a low-grade glioma, infarction, contusion, demyelinating process, or resolving hematoma.

This patient's history of first-time seizure, her parents' history of emigrating from Central America, the girl's normal physical findings, and the brain MRI images led to the strong suspicion of NCC. Her EEG tracing was normal. Serology for *Toxoplasma*, cytomegalovirus, and human immunodeficiency virus was negative. A tuberculosis skin test was negative. Empiric antihelminthic therapy was begun pending *Cysticercus* titers. This patient's enzyme-linked immunosorbent assay (ELISA) titers were in the equivocal range. A probable diagnosis

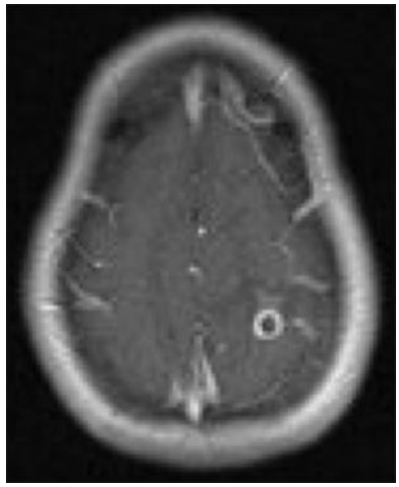

Figure 5. Brain MRI shows a solitary 9-mm ring-enhancing lesion in the left superior parietal lobe.

of NCC was made based on the clinical presentation, highly suggestive neuroimaging results, and contact with endemic hosts.

The Condition

The pork tapeworm (*Taenia solium*) is responsible for a great burden of disease in the developing world and is being seen with greater frequency in the United States. Human infection occurs following ingestion of eggs from a tapeworm-infected host via the fecal-oral route. Cysticercosis occurs when the larval form of *T solium*, known as *Cysticercus cellulosae*, invades human tissue. Once in the GI tract, the eggs hatch and release oncospheres into the vascular system and lymphatics that spread to other tissues.

NCC refers specifically to infection of the CNS. Once passing the blood-brain barrier, the oncospheres reach adult size within a few weeks. However, full neurologic symptoms may not present for years. In the brain, the parasite gradually may become inactive and calcify from a local inflammatory response or remain active, with continued cyst production.

NCC is the leading cause of acquired epilepsy worldwide, accounting for up to 70% of all new-onset seizures in the developing world. A recent outbreak among New York orthodox Jews demonstrated that ingestion of pork or recent travel to endemic areas is not required for NCC infection.

Clinical Features

Children who have NCC present with seizures of variable type, depending on the location of the *Cysticercus* granuloma. The most common manifestation is a partial seizure, with or without secondary generalization, due to local tissue inflammation associated with a solitary enhancing lesion. EEG may show focal signs of epileptiform activity. The seizures typically respond to antiepileptic therapy.

In addition to seizures, headaches are very common and may be the initial presenting symptom. An extraparenchymal granuloma may obstruct CSF flow, causing increased intracranial pressure and hydrocephalus. Parenchymal involvement may produce changes in school performance, mood, or personality.

Diagnosis

NCC usually is suspected when there is a history of seizures and identification of a ring-enhancing lesion or lesions on neuroimaging studies. Serologic tests for cysticercosis have been limited in the past due to poor sensitivity. Patients who have solitary or inactive calcified lesions may not demonstrate elevated titers by ELISA. This patient's titers by ELISA were in the equivocal range. Electroimmunotransfer blot assay has shown superiority to ELISA (sensitivity 86%, specificity 92%). CSF studies are not required for diagnosis.

Treatment and Prognosis

Treatment of NCC remains controversial. Factors to be considered include the location, number, and size of cysts as well as the degree of cyst activity. Until recently, very few controlled studies have investigated the efficacy of different treatments. Foremost, seizures should be controlled with antiepileptic drug therapy. Typically, such drugs may be discontinued after the patient has been free of seizures for 1 year and lesions are resolving on neuroimaging studies.

Hydrocephalus and increased intracranial pressure require neurosurgical management.

The treatment of a solitary CNS lesion remains controversial. Recent evidence suggests that inactive calcified lesions do not require antihelminthic treatment because viable cysts are not present.

Albendazole (15 mg/kg) in two daily doses for 14 days is the recommended therapy for patients who have active lesions. Systemic corticosteroids may be used before starting albendazole to ameliorate the adverse effects of cysticidal therapy. The addition of systemic corticosteroids in patients who do not have hydrocephalus has been shown to decrease the inflammatory response following antihelminthic treatment, thereby limiting emergent complications such as seizures or increased intracranial pressure. Patients who have single enhancing lesions have a 15% recurrence rate of seizures following antihelminthic therapy at 5 years. Patients who have extraparenchymal lesions have an increased risk for developing hydrocephalus and, therefore, a less favorable prognosis.

Lessons for the Clinician

- NCC is the most common cause for unprovoked seizures in the developing world.
- NCC should be suspected in an otherwise healthy older child presenting with a first unprovoked seizure and a ring-enhancing lesion.
- A history of pork ingestion or exposure is not required for diagnosis, although epidemiologic risk factors should be ascertained on admission.
- Active NCC lesions should be treated with albendazole and corticosteroids; inactive lesions do not require treatment. Generally, children who have single solitary lesions from NCC have a favorable prognosis.

(*Gurpreet Vidwan, MD, Levine Children's Hospital, Charlotte, NC, Winsley Rose, MD, Christian Medical College, Vellore, India*)

To view Suggested Reading lists for these cases, visit http://pedsinreview.aappublications.org and click on Index of Suspicion.

Index of Suspicion

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Ethics for the Pediatrician: The Ethics of Complementary and Alternative Medicine

Brenda J. Mears

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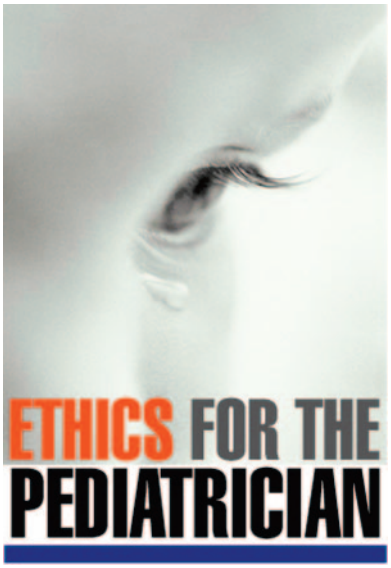

The Ethics of Complementary and Alternative Medicine

Brenda J. Mears, MD*

Author Disclosure
Dr Mears has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Introduction

Complementary and alternative medicine (CAM) is being used by a significant segment of society. To aid families who are using or considering CAM, pediatricians need to educate themselves about the available modalities and make this information available to these families. (1)(2)

The 2007 National Health Interview Survey from the Centers for Disease Control and Prevention's National Center for Health Statistics estimated that 38.2% of adults and 11.8% of children had used some type of CAM in the preceding 12 months. (3) The rates may range as high as 70% in some groups. (4) In one survey, 87% of pediatricians had been asked by patients or parents about CAM, although as many as 66% may not tell their physicians when they do use CAM. (4)(5) Some of the cost of this care may be covered by insurance or government programs, but much is paid directly by families.

Types of CAM

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health defines CAM as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine." Everything from whole medical systems such as homeopathy or naturopathy; mind-body medicine such as meditation, prayer, yoga, biofeedback, hypnosis, guided imagery, and art or music therapy; biologically based practices such as herbs, vitamins, and nutritional therapy; manipulative and body-based practices such as chiropractic or massage; and energy medicine such as biofield and bioelectromagnetic therapies has been considered CAM by some people. (6)

When families use *alternative* medicine, these therapies are used instead of conventional medicine. *Complementary* medicine uses these therapies as well as conventional medicine. *Integrative* medicine blends conventional medicine and complementary therapies for which there is evidence of safety and effectiveness. The boundaries may blur, and some therapies once believed to be CAM, such as cognitive behavior therapy or prebiotic and probiotic use, now are considered by many to be conventional. (6)

Conventional medicine is intended to be based on knowledge of safety and efficacy obtained from randomized, controlled trials and attempts to avoid treatments that are not supported by such evidence; CAM therapies may have fewer supporting data. In practice, many activities in both conventional medicine and CAM lack rigorous evaluations. This is not a reason to exempt either CAM or conventional medicine from attempts to improve the evidence supporting the care given to patients. NCCAM funds and conducts many of the increasing number of scientific studies of CAM. (6)(7)

Concerns about using CAM include the risk that it will be used by someone who has a serious disease in place of a beneficial, well-studied treatment whose risks and benefits are known. If families do not tell clinicians that they are using CAM,

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clinicians are unable to monitor for possible problems. The CAM practitioner may or may not be trained and licensed. Specific CAM remedies, such as some herbs, are toxic (mistletoe and skullcap). St John's wort and garlic may affect the P450 system. Even therapies believed to be nontoxic may have poor quality control in their production. Vitamin overdose, chemical burns, lead toxicity, and vertebral artery thrombosis after chiropractic manipulation all have been reported. (8)(9)

Legal Questions

Legal questions about CAM fall into several categories: reporting of abuse and neglect, malpractice liability, disciplinary issues of state licensing, and possibly, issues of fraud. Caregivers who use CAM are not relieved of their duty to seek necessary medical care for the children in their care. It may, at times, be unclear if reliance on CAM is abuse or neglect, but if parents are using alternative therapies for life-threatening illnesses for which effective conventional therapies are available, physicians must notify child protective services. Generally, courts allow parental choice and are reluctant to overrule parents unless the situation is life-threatening. Although the use or provision of CAM is not necessarily negligent, the same rules of negligence apply to both CAM and conventional medicine. If the patient is injured and the practitioner has not conformed to an appropriate standard of care, these can be grounds for either a civil lawsuit or professional discipline. (8)

Ethical Considerations

Why would families choose to use therapies that may be unproven, risky, and expensive? Although the goals of both conventional medicine and CAM may include prevention of disease, promotion of health, relief of symptoms, improved quality of life, and health promotion, families may feel that their own goals are not being met by conventional medical practitioners. Some families are dissatisfied with the complex technology and adverse effects of conventional medicine. They may perceive a "natural" treatment as being safer. Conventional medical practitioners recognize the necessity of physician-patient relationships for successful treatment, but families may see the emphasis on studies in conventional medicine as undervaluing relationships and may want care that is more empowering and patient-centered. In cases of chronic or terminal illness, they may believe that any approach is worth a trial.

When a pediatrician needs to offer an ethical response to concerns about the use of CAM, a number of factors must be considered, including the patient, the illness, the conventional treatments being used, the proposed CAM treatment, and practitioner and family understanding. The four principles of Beauchamp and Childress—autonomy, nonmaleficence, beneficence, and justice—provide an approach to organizing this decision-making, even when multiple principles apply and may be in conflict in a single situation. (10)

Autonomy

Personal autonomy is the right of a competent patient to make decisions about personal medical care consistent with personal values. This right includes the ability to choose or refuse treatment that may be conventional, nonconventional, experimental, dangerous, or ineffective. Rules for truth telling, disclosure, and informed consent derive from our ideas about autonomy.

Before any diagnostic or therapeutic procedures are performed, informed consent must be given. An adequate informed consent requires the decision-maker to have all relevant information about the risks and benefits of possible management options, including treatment and nontreatment, with both conventional and relevant CAM modalities. This disclosure should include the rare and serious as well as the common and mild problems. Some families want much more information, including that which may not be available. For pediatric patients, informed consent normally is obtained from the parents, and assent is obtained from the child, when appropriate. Withholding available information undermines the trust among the family, patient, and doctor and interferes with the adequacy of the informed consent. (11)

Beneficience

Beneficence is the duty to promote good and act in the best interest of the patient. This principle implies an obligation to protect and defend the rights of others by our actions. Clinicians have an obligation to help patients achieve the goals of medicine, such as promoting health and relieving suffering, even when the patient and medical practitioner differ in the prioritization of these goals and the preferred methods of achieving such goals. The principle of beneficence requires clinicians to promote understanding and respect for patients' religious, cultural, and health-related beliefs and values.

Nonmaleficence

Nonmaleficence is the duty to protect and to not harm patients. Although many procedures, whether conventional or nonconventional, cause pain, clinicians should cause no more discomfort than necessary, cause

no offense, and avoid causing harm through negligence or carelessness.

Justice

Justice is fairness. Social benefits and burdens should be distributed fairly, with "access to medical care for all people." If some CAM therapies are safe, effective, and appropriate, patients should have access to them. If others are not helpful, resources used for them are not available for other, more beneficial management. Clinicians should consider and act fairly when the interests of various individuals are in conflict. (2)

Conclusion

In visits with patients and families, clinicians should obtain histories, perform physical examinations, and secure documentation, including asking about the use of various CAM therapies. This knowledge is essential to evaluating and counseling families about their children's health. Clinicians never should dismiss the concerns of the family about management options and should avoid defensive reactions. Pediatricians must educate themselves and their families about the risks and benefits of various treatments being considered, whether conventional, alternative, complementary, or integrated. Family goals may lead to choices that differ from those who provide the health care, but if the assumption is made that there is no negligence or abuse involved in their choices, any treatment should be directed at meeting those goals. All discussions and consents need to be as informed as possible and documented clearly, whether advice has been accepted or rejected by the family. All responses of all patients to the chosen therapies of any type should be monitored. If a family chooses a treatment outside the clinician's scope of practice, he or she still can evaluate responses, even if unable to refer or provide treatment. If the physician and family are unable to agree on management, but the involvement of child protective services is not appropriate, transfer of the family to another pediatrician may be necessary.

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Ethics for the Pediatrician: The Ethics of Complementary and Alternative Medicine

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In Brief: Nonalcoholic Fatty Liver Disease

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In Brief

Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is a generic term encompassing a spectrum of disorders defined by their histopathology. On one end of the continuum is simple macrovesicular steatosis, which is defined by large fat droplets within hepatocytes. Over time, however, simple steatosis may progress. When inflammation is present, with or without fibrosis, the condition is known as nonalcoholic steatohepatitis (NASH). The far end of the spectrum is frank cirrhosis. All of the entities constituting NAFLD are associated with obesity and insulin resistance and, by definition, occur in the absence of alcohol consumption.

First described in the pediatric literature just over 25 years ago, NAFLD today is recognized as an increasingly significant cause of liver disease. Estimates of the overall prevalence of NAFLD vary, based on the method of detection, but it likely is present in approximately 9% of all children and in up to 80% of obese children. With the obesity epidemic and increased physician awareness, these figures are almost sure to increase.

Currently, the average age at diagnosis is 12 years, with the earliest reported cases at about 2 years of age. Evidence also suggests that children are developing more advanced stages of NAFLD at earlier ages. In 2006, for example, it was estimated that 25% of children who had NASH were younger than 10 years of age. Several recent case reports have described toddlers who have NASH and even have linked NASH to the formation of cirrhosis in children younger than 10 years.

Boys are approximately 40% more likely than girls to have steatosis, even after controlling for confounding factors such as body mass index (BMI) and ethnicity. NAFLD is more common in certain ethnic groups, with the highest prevalence seen among Hispanic children. Hispanic adolescents specifically are more likely to develop significant liver fibrosis. Surprisingly, despite having higher rates of risk factors such as insulin resistance and obesity, African American children have the lowest prevalence of fatty liver disease. Asian and white children have intermediate prevalences.

NAFLD results from accumulation of lipids within the liver and is linked closely to the hyperinsulinism and decreased insulin sensitivity associated with obesity. Insulin resistance causes a total body increase in lipolysis; the circulating free fatty acids produced are ultimately taken up by hepatocytes. Hyperinsulinism, on the other hand, contributes to steatosis via two routes: increasing fatty acid synthesis through increased glycolysis and decreasing hepatic production of apolipoprotein B-100, the principal protein responsible for fatty acid exportation. With excess production and decreased exportation, excessive fat accumulates within hepatocytes.

Although the exact pathogenesis of NASH is unclear, a "two-hit" mechanism seems likely. Fat accumulation within hepatocytes, as described previously, is the first "hit." Steatosis renders hepatocytes more susceptible to injury and is a prerequisite for developing the inflammation and fibrosis found in NASH.

In response to steatosis, hepatocytes have two primary mechanisms to dispose of excess lipids: mitochondrial beta oxidation converts fatty acids into adenosine triphosphate and ketone bodies and triglycerides are secreted via apolipoprotein B-100 into the bloodstream as very low-density lipoprotein. However, in NAFLD, apolipoprotein B-100 concentrations are decreased and the triglyceride load to the liver is increased dramatically. As such, lipid metabolism is shunted toward mitochondrial beta oxidation, which can produce a high burden of free radicals. The oxidative stress from beta oxidation and other pathways is the likely second "hit" in the pathogenesis of NASH.

Patients who develop NAFLD often

are asymptomatic, although about one third complain of vague right upper quadrant pain. On initial diagnosis, acanthosis nigricans is found in up to 50% of affected children, and hepatomegaly, although often difficult to appreciate, is present in 40% to 50%. Other metabolic abnormalities such as hyperinsulinemia and dyslipidemia (specifically high triglyceride values) are especially common. Although 90% of children who have NAFLD are obese (as defined by a BMI ≥95th percentile), 10% have the disease from other causes. Thus, patients who have normal BMIs still may have NAFLD.

The diagnostic approach to NAFLD varies among pediatric gastroenterologists. Liver histology obtained from a biopsy is the gold standard in diagnosis, but the procedure can be associated with significant morbidity and even mortality. Therefore, the decision to obtain a biopsy should not be made lightly, and the procedure should be undertaken only when clinically justified and necessary.

Several screening tests for NAFLD are available. An elevated serum alanine aminotransferase (ALT) value is the most helpful and, when elevated, often is two to three times the upper limit of normal. However, children can have hepatic steatosis or even NASH with normal or only mildly elevated ALT values.

Ultrasonography is another common screening tool. Approximately 50% of abdominal ultrasonography performed in obese patients demonstrates diffuse, homogeneous, increased liver echogenicity. This finding can be associated with fatty infiltration, inflammation, or fibrosis, making this imaging modality an insensitive test. Yet, when coupled with an increased serum, ALT concentration in the correct clinical picture, ultrasonography may be highly suggestive of, but not definitive for, NAFLD. Serum transaminases, with or without ultrasonography, therefore, should be assessed as part of the evaluation of an obese child or if fatty liver disease is suspected. Other noninvasive imaging modalities such as computed tomography scan and magnetic resonance imaging have not yet been validated against liver histology and are largely nonspecific.

Particularly in the setting of obesity, practitioners must be wary of assuming a diagnosis of NAFLD based solely on an elevated serum ALT value, suggestive ultrasonography, or a combination of the two. Other causes of liver disease, including infectious, metabolic, nutritional, immunologic, or pharmacologic, must be excluded. As a general rule, any child who has persistently elevated transaminase values should be referred to a pediatric gastroenterologist for additional evaluation.

Children can develop cirrhosis from NAFLD and may develop hepatocellular carcinoma in adulthood. Fatty liver disease also has necessitated transplantation as early as adolescence. Nevertheless, data on disease progression are limited. It is unclear, for example, how frequently children advance from simple steatosis to steatohepatitis and, ultimately, to cirrhosis. The severity of baseline liver histology, however, likely is predictive. A disheartening statistic is that 5% to 10% of patients present with advanced fibrosis at the time of pathologic diagnosis.

Very few treatments are available for NAFLD. Lifestyle changes, particularly diet and exercise, are the most widely recommended interventions but should be undertaken relatively slowly because rapid weight loss can worsen liver disease acutely. In small studies, a mere 10% decrease in excessive body weight normalized serum transaminase values. Even so, it is unclear whether a decrease in transaminase concentrations is associated directly with improvement in pathology or disease progression.

The use of medications for NAFLD is an area of ongoing research. In particular, metformin appears to hold promise, having been shown to improve transaminase concentrations, decrease hepatic fat quantities, and improve insulin resistance in a small cohort of children. However, there currently is not enough evidence to justify the use of metformin specifically for pediatric NAFLD. Other medications studied show no significant efficacy. Additional research is needed regarding disease pathogenesis, noninvasive diagnostic modalities, and pharmacotherapy.

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