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Cover: The artwork on the cover of this month's issue is by one of the winners of our 2007 Cover Art Contest, 12-year-old Yolanda Sanche of Chicago, Ill. Yolanda's pediatrician is Denise Cunill, MD.

Herpes Simplex

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Drs Chayavichitsilp,
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to this article. This
commentary does
contain a discussion
of an unapproved/
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Objectives After completing this article, readers should be able to:

1. Characterize the epidemiology of herpes simplex virus (HSV) infection, including mode of transmission, incubation period, and period of communicability.
2. Recognize the difference in clinical manifestations of HSV1 and HSV2 infection.
3. Diagnose various manifestations of HSV infection.
4. Describe the difference in the clinical manifestations and outcome of HSV infection in newborns and older infants and children.
5. Discuss the management of HSV infection.
6. List the indications and limitations of oral acyclovir treatment for HSV infection.

Introduction

HSV causes a contagious infection that affects approximately 60% to 95% of adults worldwide. HSV1 and HSV2 primarily infect human populations. HSV1 is associated chiefly with infections of the mouth, pharynx, face, eye, and central nervous system (CNS), and HSV2 is associated primarily with infections of the anogenital region, although both serotypes may infect any area. (1)

Epidemiology

Most adults are infected with HSV and carry latent viruses, but the serotype, severity of symptoms, and mode of transmission vary with age. Children are infected primarily with orolabial HSV1 by 5 years of age, with infection rates of 33% in populations that are of lower socioeconomic status and 20% in those who have improved socioeconomic status. By adulthood, HSV1 affects 70% to 80% in the lower socioeconomic population and 40% to 60% in the higher socioeconomic population. (1) Globally, the prevalence of HSV1 increases consistently with age, reaching 40% by age 15 years and increasing to 60% to 90% in older adults. (2) In the United States, the prevalence of HSV1 increases consistently with age, from 26.3% in 6- to 7-year-old children and 36.1% in 12- to 13-year-old children to 90% among those older than 70 years. (2)(3) Of note, the overall prevalence of HSV1 in the United States has been shown to be decreasing over time. (3)

Worldwide, the prevalence of HSV1 infection is greater than HSV2 infection in most geographic areas. HSV2 primarily is sexually transmitted and, therefore, is not as common in young children. However, HSV2 can be transmitted from mother to neonate during pregnancy, with a neonatal incidence between 1 in 3,000 and 1 in 20,000 live births and approximately 1,500 new cases in the United States annually. Approximately 2% of women acquire genital herpes during pregnancy, and about 20% to 30% of pregnant women are seropositive for HSV2. (4) The prevalence of HSV2 varies across country, sex, and age. HSV2 prevalence is highest in areas of sub-Saharan Africa and parts of Central and South America. The prevalence usually is lower in western and

Abbreviations

CNS:	central nervous system
CSF:	cerebrospinal fluid
DFA:	direct fluorescent antibody
HAEM:	HSV-associated erythema multiforme
HHV:	human herpesvirus
HSV:	herpes simplex virus
IV:	intravenous
PCR:	polymerase chain reaction
SEM:	skin, eye, and mouth
STI:	sexually transmitted infection
VZV:	varicella-zoster virus

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southern Europe than in northern Europe and North America. The lowest rates of HSV2 prevalence are found in Asia.

Generally, the prevalence is higher in women than in men and increases with age from negligible levels in children younger than 12 years to 20% to 40% by the age of 40 years and as high as 80% among higher-risk populations. (1)(2)(5)(6) In the United States, the prevalence of HSV2 infection in African Americans is much higher than in whites or Mexican Americans. Although time trends in HSV prevalence are limited, most studies suggest that the prevalence of HSV2 has increased over the past few decades in countries such as the United States from 16.0% in the late 1970s to 20.8% in the early 1990s; in other populations, HSV2 prevalence has either remained stable or decreased. (2)

As stated previously, HSV2 is associated primarily with infections of the anogenital region, whereas HSV1 is found extragenitally. Recent studies, however, have shown a 30% increase in the prevalence of HSV2 infection, (7) with HSV2 being as common as HSV1 in the extragenital regions except for the orofacial area. Furthermore, HSV1 appears to be increasing in prevalence in the anogenital region, previously known to be infected predominantly by HSV2.

Etiology

There are more than 80 herpesviruses, eight of which are capable of infecting humans. In addition to HSV1 and HSV2, varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, human herpesviruses (HHV6 and HHV7), and Kaposi sarcoma-associated herpesvirus (HHV8) can infect humans. All herpesviruses are enveloped, double-stranded DNA viruses that have highly organized genomes encoding more than 84 polypeptides. (6) Although the DNA sequences of HSV1 and HSV2 are very similar, the proteins within the envelope allow serologic distinction between the two.

Transmission

Infection is transmitted primarily through exposure to mucous membranes or skin that have active lesions or to mucosal secretions of an individual who has an active HSV infection. The virus is transmitted most easily through saliva and can remain stable outside of the host for short periods of time, allowing transmission for some time after direct mucocutaneous contact with the virus. HSV also can be transmitted through respiratory droplets or by exposure to mucocutaneous secretions from an asymptomatic person who is shedding virus. Shedding

refers to the presence of viruses outside of the cells on the skin surface, despite the absence of clinical signs. (1)

The initial or primary HSV1 or HSV2 infection usually has an incubation period of approximately 4 days, but can range from 2 to 12 days. This is followed by an active viral shedding period that lasts at least 1 week and up to several weeks. Most patients who are primarily infected with HSV are asymptomatic. Therefore, the virus still can be actively transmitted during the period of incubation and viral shedding without the occurrence of active skin lesions. (1)

After initial infection, the virus usually remains latent, persisting within the sensory ganglia of the autonomic nervous system, and the infection can be considered incurable. Within the autonomic ganglia, the virus replicates while evading detection by the host immune system. (1)(6) HSV1 resides most commonly within the trigeminal ganglion, due to its primary target site in and around the oral areas; HSV2 primarily remains in sacral ganglia after infection of the genital region. Once triggered to reactivate by an internal or external stimulus, including stress, exposure to sunlight, fever, and menstruation, the virus can travel along the sensory nerve and reactivate in the same mucocutaneous region as the initial infection. Symptoms normally last for a shorter period of time than for the initial infection, and viral shedding only lasts 3 to 4 days. On average, reactivation of HSV occurs during approximately 1% of the days in the life of patients infected previously. (8)

Diagnosis

Several methods are employed to diagnose the presence of HSV infection, each having varying degrees of selectivity, sensitivity, cost, and utility. The main clinical method for diagnosing primary HSV1 infection is recognizing the classic presentation of herpetic lesions in or around the oral cavity. Monomorphous, grouped vesicles on an erythematous base evolve into coalescing, crusted papules and plaques within 1 to 3 days. The lesions have a propensity to erode or ulcerate. Initial infection can lead to an extensive gingivostomatitis. In contrast to HSV1, the initial diagnosis for HSV2 can be more difficult because the classic signs of genital herpes, herpetic ulcers in and around the genital area, may not be present. In neonates, the presence of vesicular lesions should raise high suspicion for HSV infection.

Laboratory evaluations can be used to confirm an initial diagnosis or further investigate a suspicion of HSV infection. The gold standard for laboratory diagnosis is the viral culture. The viral culture technique can be employed only with active lesions and is obtained best by

vigorously swabbing the base of an unroofed vesicle. The swab is inoculated into a prepared cell culture, and the inoculated cells are observed for characteristics of HSV infection, including multinucleated giant cells and desquamated epithelial cells with intranuclear inclusions. Such findings usually are observed within 2 to 7 days after inoculation and can confirm the presence of HSV infection. If the inoculated cell culture is devoid of characteristic signs of HSV infections for more than 15 days, the sample is reported as negative. Although this method offers a relatively rapid and effective method of diagnosing HSV infection, it can be limited by the quality of swabbing and culture techniques.

The Tzanck smear is a rapid and reasonably priced diagnostic test that can confirm the presence of HSV infection. Cells scraped from the base of a freshly opened vesicle are stained and evaluated for the characteristic cytopathology of HSV infected cells, including multinucleated giant cells and eosinophilic intranuclear inclusions (Fig. 1). Although the test can confirm the presence of HSV or VZV, it cannot differentiate between the two herpes serotypes and, therefore, cannot diagnose HSV1 or HSV2 infection definitively. In addition, the sensitivity and specificity of the test are highly variable, depending on the evaluator. An experienced clinician, such as an infectious disease specialist or pathologist, should interpret test results because the findings may be subtle. With the increasing availability of the direct fluorescent antibody (DFA) technique, the Tzanck smear has decreased in popularity as a diagnostic alternative.

DFA testing is an immunohistochemistry technique that uses a specific antibody to identify the presence of

viral antigens. The antibody is tagged with fluorescent agent and forms an antigen-antibody complex with HSV antigens present within a tissue or smear specimen. The process can be performed with cytologic preparations, such as the Tzanck smear, as well as virally inoculated cell cultures. In addition, DFA may be employed to serotype the HSV infection. Because DFA testing is rapid, sensitive, inexpensive, and virally selective, it often is used to substantiate clinical suspicion and determine serotype.

A punch, shave, or wedge tissue biopsy also may be used to detect the presence of HSV infection and is especially helpful when a suspicious lesion is old or atypical. The biopsied cells are observed microscopically to detect degenerative cytopathologic changes commonly associated with the infection. The degenerative changes present in cells infected with HSV1 and HSV2 also are observed in cells infected with VZV. Thus, the specificity of the technique is low, and the test cannot be used to serotype the infection.

Amplification of viral DNA using polymerase chain reaction (PCR) is another method for detecting the putative presence of viral DNA. This method is particularly useful for detecting the presence of HSV in the cerebrospinal fluid (CSF) of patients suspected of having herpes encephalitis. As HSV PCR becomes more readily available and less expensive, it has the potential to become the most widely used means of detecting HSV for all types of infection because it is rapid, highly reliable, and valid.

Serologic assays are employed to detect the presence of HSV antibodies when other techniques are impractical or ineffective. Such assays take longer to complete than other techniques and should be considered primarily for diagnosing recurrent infections, in the presence of healing lesions and the absence of active lesions, or when partners of persons who have clinical herpes are at risk. Sera are collected at two separate times; acute serum is obtained within 3 to 4 days after the onset of the initial symptoms and convalescent serum is gathered several weeks after the symptoms have abated. To confirm a diagnosis of primary HSV infection, the acute sample should be devoid of HSV-positive antibodies due to the delayed humoral response, and the convalescent sample should demonstrate the presence of both immunoglobulin G and M antibodies to HSV proteins. If any quantities of antibodies are observed in the acute sample, primary infection is ruled out and the diagnosis is recurrent herpes infection. The absence of antibodies in both samples indicates a negative test, which should be verified later by another serologic assay. In the absence of herpetic lesions, traditional serologic assays cannot deter-

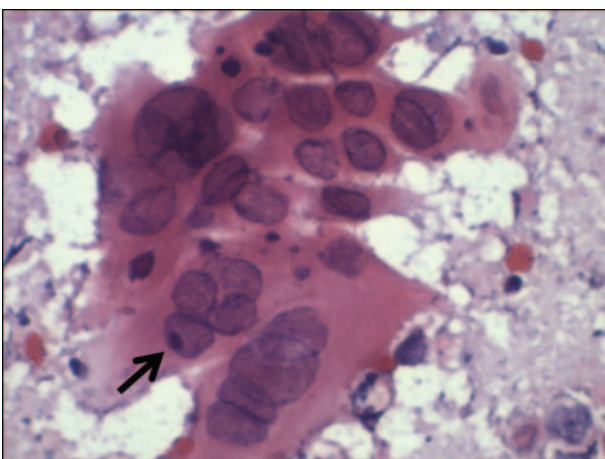


Figure 1. A positive Tzanck smear showing a multinucleated giant cell and intranuclear inclusions (arrow). Courtesy of Dr Robert O. Newbury.

mine the serotype or whether the site of infection is oral or genital. However, newer type-specific serologic assays can be performed to test for antibodies to both HSV1 and HSV2 proteins.

Several transport media are available for effective viral transport after collection of the specimen, including swabs, liquid media, and cell cultures. Studies suggest that although there are slight differences in the survivability of both HSV1 and HSV2 in different media, most media are effective as long as the temperature is tightly controlled, preferably at 39.2°F (4.0°C), and transport times are kept to a minimum, preferably less than 24 hours and no greater than 48 hours. (9) Survival of the virus at temperatures greater than 39.2°F (4.0°C) and transport times greater than 48 hours for all transport media is variable and more dependent on viral concentration and accurate laboratory techniques.

Clinical Manifestations

The clinical presentation of HSV infection is variable and dependent on method of transmission, age, and immunocompetency of the host. Cutaneous lesions usually consist of small, monomorphous vesicles on an erythematous base that rupture into painful, shallow, gray erosions or ulcerations with or without crusting. (10) The skin lesions typically are preceded by prodromal symptoms such as burning and paresthesia at the site, lymphadenopathy, fever, malaise, myalgia, loss of appetite, and headaches. Most initial infections are subclinical and may be unrecognized. Recurrent infections due to reactivation of the latent viruses in the dorsal root ganglia are more localized, milder, and shorter in duration. They tend to occur following triggers such as stress, menstruation, exposure to sunlight, and fatigue. Both primary and recurrent HSV infections can manifest on any mucocutaneous surface. Table 1 summarizes the clinical manifestations, differential diagnoses, and recommended treatments of herpetic infections occurring after the neonatal period.

Herpetic Gingivostomatitis

Herpetic gingivostomatitis presents as multiple round ulcers or superficial erosions commonly affecting the palate, tongue, and gingivae. It is caused much more commonly by HSV1. Patients may present with the typical prodromal symptoms, followed by classic vesiculoulcerative lesions. Children may present with diffuse erythema and swelling of the gingiva, drooling, foul-smelling breath, and anorexia. Such nonspecific signs and symptoms can be caused by a wide range of conditions, including Coxsackievirus infections, erythema multi-

forme, pemphigus vulgaris, acute necrotizing ulcerative gingivitis, and most commonly, aphthous stomatitis. Aphthous stomatitis can be differentiated from herpetic gingivostomatitis by the absence of a vesicular stage, prodrome, and systemic signs and symptoms. The major complication of herpetic gingivostomatitis is dehydration in children whose painful lesions result in poor fluid intake. Thus, pain control and sufficient rehydration comprise the mainstay of management.

Herpes Labialis

Herpes labialis is the most common manifestation of HSV1 infection. Because most initial infections are asymptomatic and may be unrecognized, recurrent orofacial herpes (commonly called fever blisters or cold sores) typically is the initial manifestation in children and young adults. The outer vermilion border is a common location, and the crusted lesions often are confused with staphylococcal or streptococcal impetigo (Figs. 2, 3). Secondary bacterial infections with *Staphylococcus* or *Streptococcus* also may occur and are characterized by honey-colored crusting on top of the classic herpetic lesions. Treatment with oral acyclovir can be effective if started within 1 to 2 days of prodromal symptoms. Chronic suppressive therapy with an oral antiviral medication can reduce the frequency of recurrences and is recommended for patients who experience six or more outbreaks per year. (8) Topical acyclovir is ineffective in immunocompetent hosts and, therefore, is not recommended.

Genital Herpes

Genital herpes (Fig. 4) most commonly is caused by HSV2, although the proportion due to HSV1 has been increasing recently. (1) This sexually transmitted infection (STI) is associated with risk factors such as lower socioeconomic status, sexual promiscuity, geography, race, and education. (1) Differential diagnoses include other STIs such as syphilis, chancroid, condyloma acuminata, and lymphogranuloma venereum, and non-STIs such as *Candida* infection, scabies, lichen planus, lichen sclerosis, Behçet syndrome, herpes zoster, and trauma. Sexual abuse must be suspected in prepubertal children who develop genital herpes. Complications include urinary retention, psychological morbidity, and aseptic meningitis. The pathogenesis of the spread to the CNS is unclear, but two routes are possible, including the hematogenous route and direct spread from mucocutaneous sites through the peripheral nerves. Treatment with oral antiviral medication can be effective if started early. For

Table 1. Clinical Manifestations, Differential Diagnoses, and Recommended Treatments of Herpes Simplex Virus Infections

Clinical Manifestation	Differential Diagnoses	Recommended Treatment
Herpetic Gingivostomatitis	<ul style="list-style-type: none"> • Herpangina • Hand-foot-and-mouth disease • Erythema multiforme • Pemphigus vulgaris • Acute necrotizing ulcerative gingivitis • Aphthous stomatitis 	<ul style="list-style-type: none"> • Pain control and rehydration • Insufficient data regarding response to antiviral treatment, but many experts treat severe cases
Herpes Labialis	<ul style="list-style-type: none"> • Impetigo 	<ul style="list-style-type: none"> • For primary disease and recurrences, oral acyclovir has limited therapeutic benefits in immunocompetent hosts, but many experts treat severe cases • Suppression for recurrent episodes*
Genital Herpes	<p><u>Sexually transmitted infections:</u></p> <ul style="list-style-type: none"> • Syphilis • Chancroid • Condyloma acuminatum • Lymphogranuloma venereum <p><u>Non-sexually transmitted infections:</u></p> <ul style="list-style-type: none"> • <i>Candida</i> infections • Scabies • Lichen planus • Lichen sclerosis • Behçet syndrome • Herpes zoster • Trauma 	<ul style="list-style-type: none"> • Primary: Oral acyclovir 1,000 to 1,200 mg/day for 7 to 10 days • Recurrences: Oral acyclovir 1,000 to 1,200 mg/day for 3 to 5 days • Suppression*
Herpetic Keratoconjunctivitis	<ul style="list-style-type: none"> • Scleritis • Iritis • Glaucoma • Conjunctivitis • Herpes zoster 	<ul style="list-style-type: none"> • Prompt referral to ophthalmology • Trifluridine 1%, iododeoxyuridine 0.1%, and vidarabine 3% ophthalmic ointments • Suppression*
Herpetic Whitlow	<ul style="list-style-type: none"> • Bacterial felon • Paronychia • Blistering dactylitis • Burn • Impetigo 	<ul style="list-style-type: none"> • Supportive • Antiviral therapy early in the course can be considered
Herpes Gladiatorum	<ul style="list-style-type: none"> • Atopic dermatitis • Contact dermatitis • Impetigo • Tinea corporis 	<ul style="list-style-type: none"> • Avoid contact sports until lesions have become dry and firm and crusts are adherent • Suppression throughout sports season is controversial
Herpes Encephalitis	<ul style="list-style-type: none"> • Other bacterial and viral encephalitis 	<ul style="list-style-type: none"> • Intravenous acyclovir for 21 days
Eczema Herpeticum	<ul style="list-style-type: none"> • Atopic dermatitis flares • Impetigo 	<ul style="list-style-type: none"> • Intravenous acyclovir usually recommended • Oral antibiotic therapy for secondary bacterial infection • Topical emollients • Topical steroids as needed • Avoid topical calcineurin inhibitors
<p>*If recurrences involve six or more episodes per year, oral acyclovir 80 mg/kg per day or 800 to 1,200 mg/day continuously up to 12 months is recommended. Data from <i>Red Book: 2006 Report of the Committee on Infectious Diseases</i>. (8)</p>		

patients experiencing frequent recurrences (at least six episodes per year), chronic suppressive therapy with an oral antiviral is recommended. (8)

Herpetic Keratoconjunctivitis

Ocular HSV infection is the second most common infectious cause of blindness worldwide. HSV1 is the predom-



Figure 2. An early vesicle on an erythematous base at the vermillion border in herpes labialis. Reprinted with permission from Dr Sheila F. Friedlander.

inant cause. Vesicles, followed by erosion or ulceration of the cornea, appear along with purulent conjunctivitis. Differential diagnoses include scleritis, iritis, glaucoma, conjunctivitis, and herpes zoster. Prompt referral to ophthalmology is recommended to prevent complications such as permanent scarring, secondary bacterial infection, meningoencephalitis, and vision loss. Neonates afflicted with ocular HSV may have associated systemic or CNS disease. Treatment consists of both topical ophthalmic antiviral (trifluridine, vidarabine, idoxuridine) and oral antiviral medications.

Herpetic Whitlow

Herpetic whitlow presents with deep-seated swelling, erythema, and vesiculoulcerative lesions on the pulp of



Figure 3. Vesicles and crusting on the vermillion border, typical location of herpes labialis. Reprinted with permission from Dr Victoria R. Barrio.



Figure 4. Multiple monomorphous vesicles on an erythematous base on the penile shaft and scrotum that are characteristic of genital herpes. Reprinted with permission from Dr Sheila F. Friedlander.

the distal phalanx of the hand (Fig. 5). This infection occurs commonly in patients who have primary oral or



Figure 5. Herpetic whitlow, showing deep-seated vesicles grouped in clusters on the digit. Reprinted with permission from Dr Sheila F. Friedlander.

genital herpes (due to autoinoculation) and health-care workers. In children, digital/oral contact is the most common cause of herpetic whitlow. In adolescents and adults, digital/genital contact is more common, making HSV2 the predominant infectious agent of herpetic whitlow. Differential diagnoses include bacterial felon or paronychia, blistering dactylitis, burn trauma, and impetigo. (10) Oral antiviral medications are optional and are used in extensive disease.

Herpes Gladiatorum

Herpes gladiatorum occurs in those involved in contact sports such as wrestling, boxing, football, soccer, and rugby. It most commonly affects exposed areas such as the face, ears, upper extremities, and neck. HSV1 is more likely to be the agent than HSV2, due to the nature of transmission. Differential diagnoses include atopic dermatitis, contact dermatitis, impetigo, and tinea corporis. Patients who have herpes gladiatorum should avoid contact sports during outbreaks until the culture results are negative. (11) Measures to prevent transmission also should be practiced and include examining athletes for active lesions and excluding them from competition and cleaning wrestling mats with bleach for at least 15 seconds of contact time between matches. (8) The National Collegiate Athletic Association recommends that athletes not be allowed to participate until the crusts are firm and adherent. (11) If the lesions have not crusted over or the crusts are not completely dry, the possibility is high that the patient still is infectious. Cultures to verify the noninfectious state should be performed after the crusts are dry, firm, and adherent. The family of an affected patient must be informed and instructed to perform appropriate preventive measures. Suppressive therapy is likely to be effective, but data about such therapy are insufficient, and the family needs to be made aware of this limitation before the initiation of therapy.

Herpes Encephalitis and Meningitis

HSV encephalitis can be a manifestation of primary or recurrent infections. Patients present with nonspecific CNS symptoms such as altered mental status, personality changes, seizures, and focal neurologic findings. HSV meningitis is characterized by CSF pleocytosis, with lymphocyte predominance and red blood cells in the CSF. HSV also is believed to cause a rare form of aseptic meningitis, termed Mollaret syndrome, consisting of recurrent episodes of severe headache, meningismus, and fever that resolve spontaneously.

Complications include Bell palsy, atypical pain syndromes, trigeminal neuralgia, ascending myelitis, and

postinfectious encephalomyelitis. Therapy is less effective in older adults than in children. Therefore, the recommended treatment for adults (parenteral acyclovir for 21 days) also is recommended for pediatric patients who have herpes infections of the CNS. (8)

Neonatal Herpes

Neonatal herpes occurs in 1 in every 3,000 to 20,000 live births and affects approximately 1,500 to 2,000 infants per year in the United States. (8) In addition, 40% to 50% of infants born to mothers afflicted with primary genital lesions are affected compared with only 2% to 3% of those born to women undergoing recurrences. (10) Up to 70% of infants who have neonatal herpes are born to asymptomatic mothers, adding to the difficulty in diagnosing this disease.

Neonatal herpes manifests in the first 4 weeks after birth and consists of three different types based on clinical manifestations: 1) skin, eye, and mouth (SEM), 2) CNS (often presenting with seizures, lethargy, and hypotonia), and 3) disseminated (including liver, adrenal glands, lungs). Classic cutaneous lesions generally are located on the scalp, mouth, nose, and eye, where the infant's skin comes into contact with the mother's genital lesions (Fig. 6). CNS infection presents with neurologic signs such as seizures and accounts for 60% of the cases. Skin lesions also are noted. Permanent neurologic disability can affect up to 40% of survivors. Disseminated neonatal HSV is a devastating manifestation that is associated with a mortality rate of at least 50%. Infants present with multisystem involvement (shock, disseminated intravascular coagulation, and multiple organ system failure).



Figure 6. Cluster of vesicles on the forehead and periocular area characteristic of neonatal herpes simplex. Reprinted with permission from Friedlander SF, Bradley JS. Viral infections. In: Eichenfield LF, Frieden IJ, Esterly NB, eds. *Neonatal Dermatology*. 3rd ed. Philadelphia, Pa: Saunders; 2008:193–197.

The differential diagnosis of neonatal HSV infection includes bacterial sepsis and viral infections such as enteroviruses, varicella, influenza A and B, parainfluenza, and adenovirus. Incontinentia pigmenti and Langerhans cell histiocytosis also may present with vesicles and must be differentiated from HSV by using the diagnostic techniques described previously.

HSV is transmitted most commonly during delivery, but also can be transmitted in utero or through postnatal contact with the mother or other caretakers. It is not transmitted through human milk. Higher risks of transmission are associated with younger age of the mother, maternal seronegativity, the presence of genital lesions during vaginal delivery, and infant prematurity.

Because of high rates of morbidity and mortality, timely diagnosis and prompt initiation of treatment are crucial. A high degree of suspicion is required in neonates who have vesicular skin lesions, sepsis syndrome with negative bacteriologic culture results, severe liver dysfunction, fever, irritability, and abnormal CSF findings, particularly if seizures are present. Because of the low toxicity profile of the antiviral medications and the potentially severe post-HSV sequelae, it always is better to institute therapy pending culture results if significant suspicion exists.

Prevention also is crucial, although there is no consensus on the optimal prevention strategy. Pregnant mothers who are seronegative and have seropositive sexual partners should be counseled to maintain abstinence near term. For those who acquire primary genital HSV during late pregnancy, the National Guideline Clearinghouse states, "Some specialists recommend acyclovir therapy, some recommend routine cesarean section and others recommend both." (12) However, for those who have a history of recurrent genital HSV, a Cochrane review found insufficient data to support the use of prophylactic acyclovir. (13)

Congenital HSV

Congenital HSV describes an HSV2 infection of the fetus that has occurred prenatally. Infected fetuses often die in utero. However, those that survive to term typically present with vesicular lesions, chorioretinitis, microphthalmia, microcephaly, and abnormalities on brain scan.

Congenital HSV in neonates can be differentiated from neonatal HSV by the absence of signs of systemic toxicity and overwhelming sepsis in the former as well as the presence of both fetal and maternal antibodies against HSV. Other differential diagnostic considerations include congenital varicella syndrome and syphilis.

Treatment is similar to that for neonatal HSV, although the neurologic prognosis is poor, and virtually all affected infants exhibit developmental delay.

Eczema Herpeticum

Eczema herpeticum also is known as Kaposi varicelliform eruption. It is characterized by HSV infections of skin from an underlying barrier defect caused by atopic dermatitis, pemphigus, Darier disease, burn trauma, and cosmetic procedures. (1) The lesions tend to coalesce into large, superficial erosions and often are disseminated (Figs. 7 and 8). Differential diagnoses include atopic dermatitis flares, impetigo, and secondarily infected lesions. Management includes intravenous (IV) antiviral therapy, antibiotic therapy for secondary bacterial infection, and topical emollients. (10) Most experts use anti-inflammatory therapy such as topical corticosteroids in areas of atopic dermatitis once systemic antiviral therapy has been initiated. However, the use of calcineurin inhibitors is contraindicated in eczema herpeticum. (14)

Herpes in the Immunocompromised Host

HSV infections in immunocompromised individuals such as those who have hematologic malignancy, immune deficiencies, acquired immunodeficiency syndrome, and organ transplants tend to have higher risks of dissemination and longer durations of outbreaks and are less responsive to therapy. (10) Complications include esophagitis, tracheobronchitis, pneumonitis, hepatitis, pancreatitis, and adrenal necrosis. The skin lesions often



Figure 7. Eczema herpeticum, limited, showing vesicles and crusts coalescing into plaques on underlying eczematous skin in the popliteal fossa, a typical location affected by atopic dermatitis. Reprinted with permission from Dr Sheila F. Friedlander.



Figure 8. Eczema herpeticum, disseminated, showing rapidly progressing vesicles over an erythematous base that coalesced into plaques and then crusted over diffusely on the face of a young child who has underlying atopic dermatitis. Reprinted with permission of Dr Sheila F. Friedlander.

are atypical and can be extensively crusted, pustular, necrotic, or exophytic. The differential diagnosis involves herpes zoster and similar conditions, depending on the location of the outbreak. Prompt therapy with parenteral antiviral medications is critical.

HSV-associated Erythema Multiforme

HSV-associated erythema multiforme (HAEM) is a complication of HSV outbreaks that induces erythema multiforme skin lesions. Patients commonly present with fixed target or “bull’s eye” lesions distributed diffusely on the body, with a predilection for palms and soles. The lesions generally occur within 10 days of oral or genital HSV reactivation (Figs. 9 and 10). (1) This condition tends to resolve spontaneously without complications. However, patients experiencing frequent outbreaks may benefit from chronic suppressive antiviral prophylaxis.



Figure 9. Target lesions of different sizes on palm that are characteristic of erythema multiforme. Reprinted with permission of Drs Sheila F. Friedlander and Bari B. Cunningham.

Principles of Management

Management of HSV infections often incorporates both treatment and prevention of recurrences. Because of the infectious nature of the virus and the risk it poses to the neonate and immunocompromised individuals, prevention of recurrences is important and should be practiced in every patient.

Prevention

Prevention of transmission is the first step in the management of HSV infections. Patients should be educated regarding the nature of the disease, transmission through sexual and nonsexual contact, and asymptomatic shedding of the virus. Patients who have active lesions on the



Figure 10. Target lesions of different sizes on soles characteristic of erythema multiforme. Reprinted with permission of Drs. Sheila F. Friedlander and Bari B. Cunningham.

skin should avoid direct contact with others. Precautions include: 1) the use of condoms or other barrier methods during sexual intercourse for genital HSV; 2) the avoidance of contact sports, examination and exclusion of athletes who have active lesions, and cleaning of wrestling mats with bleach after every match for herpes gladiatorum; and 3) the use of condoms or abstinence for pregnant women who are seronegative whose partners are seropositive to prevent primary HSV infections during the third trimester of the pregnancy. The multiple risk factors that precipitate recurrence (eg, stress, exposure to sunlight, fever, menstruation, and trauma to the area such as dental procedures) should be addressed with patients.

In a hospital, contact precautions should be practiced by all health-care personnel for all patients possibly infected with HSV except for those whose infections are limited to encephalitis and meningitis. These measures include providing the patient with a single-patient room when possible; using gloves at all times; washing hands after glove removal; and wearing gowns during direct contact with a patient, environmental surfaces, or items in the patient's room.

Treatment

The treatment of HSV infections does not result in cure, but can attenuate the duration of the clinical course, decrease severity, prevent complications, and reduce the frequency of recurrence. Current treatments include supportive therapy and oral, parenteral, and topical antiviral medications.

SUPPORTIVE THERAPY. Supportive therapy encompasses pain control and rehydration. Such support is particularly important for children afflicted with herpes labialis and gingivostomatitis. Because of pain, patients may refuse to eat or drink, resulting in dehydration. Pain control with local anesthetics and oral or IV rehydration may be useful.

ORAL ANTIVIRAL MEDICATIONS. The first-line oral antiviral medication for children is acyclovir. Alternatives include valacyclovir and famciclovir, although their use in children had not been approved by the United States Food and Drug Administration as of July 2008. Oral acyclovir is indicated in primary genital HSV infection when treatment is started within 6 days of disease onset and can shorten the duration by 3 to 5 days. In HSV recurrences, initiating oral acyclovir within 2 days of onset shortens the duration only by an average of 1 day. The recommended dose is 1,200 mg/day (maximum of 80 mg/kg per day) for 7 to 10 days in initial infections and for 5 days in recurrences.

Chronic suppressive therapy with oral acyclovir is indicated for patients experiencing recurrence of genital, oral, or ocular HSV infection that involves six or more episodes per year. The recommended pediatric dose is 80 mg/kg per day in three divided doses, with a maximum of 1,000 mg/day for a maximum of 12 months. One study has shown that acyclovir at a dose of 400 mg twice a day chronically can suppress HAEM attacks in most patients. (15)

Acyclovir-resistant strains of HSV must be suspected in patients experiencing worsening disease despite acyclovir therapy, particularly in immunocompromised patients. Foscarnet is the recommended therapy in this case.

PARENTERAL ANTIVIRAL MEDICATIONS. IV acyclovir therapy is reserved for cases having the potential for severe complications. Such situations include any neonate who has HSV infection, mucocutaneous HSV infections in immunocompromised hosts, eczema herpeticum, and HSV encephalitis. The recommended dose is 60 mg/kg per day for 14 days in newborns who have SEM disease and 21 days in other neonatal HSV infections and HSV encephalitis (Table 2).

Acyclovir is known to cause nephrotoxicity. Therefore, it is important to calculate the dose based on ideal

Table 2. Management of Neonatal Herpes

Manifestation	Treatment
Skin, eyes, and mouth	Intravenous acyclovir 60 mg/kg for 14 days
Disseminated and central nervous system	Intravenous acyclovir 60 mg/kg for 21 days
Ocular involvement	Add trifluridine 1%, iododeoxyuridine 0.1%, and vidarabine 3% ophthalmic ointments
Asymptomatic neonates born to mothers who had primary genital infections	Empiric acyclovir therapy pending culture results*
*Not approved by the United States Food and Drug Administration; some controversy exists.	

weight, hydrate the patient well, and monitor urine output and serum creatinine values.

TOPICAL ANTIVIRAL MEDICATIONS. Although commonly prescribed by many physicians, topical antiviral medications such as acyclovir ointment are not recommended to treat most mucocutaneous HSV lesions because such therapy does not reduce the severity or duration of infections in immunocompetent hosts. Topical therapy is recommended in immunocompromised patients because it has been shown to accelerate the healing of lesions.

Ophthalmic antiviral medications, including 1% trifluridine, 0.1% idoxuridine, and 3% vidarabine, are indicated for treatment of ocular HSV and neonatal HSV with SEM involvement.

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Summary

- HSV infection is a multisystem disease characterized by early and often classic skin manifestations. Recognition of the common presentations of mucocutaneous HSV infections can lead to rapid diagnosis and timely treatment.
- The goal of management is to reduce disease severity and prevent recurrences as well as transmission to others through patient education and antiviral therapy.
- HSV1 is associated primarily with infections of the mouth, pharynx, face, eye, and CNS; HSV2 is associated primarily with infections of the anogenital region, although both serotypes may infect any area. (1)
- Based on strong research evidence, transmission of HSV is primarily through exposure to mucocutaneous surfaces with active lesions or viral shedding. (1)
- Based on strong research evidence, the primary method of diagnosis is recognition of the classic presentation of herpetic lesions on mucocutaneous surfaces, but the gold standard of diagnosis is viral culture. (1)
- Based on strong research evidence, empiric treatment of neonatal HSV with acyclovir is recommended if there is a strong clinical suspicion despite the absence of active lesions. (8)
- Based on strong research evidence, suppression therapy with oral acyclovir is beneficial for individuals who have six or more episodes per year of herpes labialis, keratoconjunctivitis, or genital herpes. (8)
- Based on strong research evidence, parenteral acyclovir is recommended in neonatal HSV, HSV in immunocompromised patients, eczema herpeticum, and HSV encephalitis. (8)
- Based on some research evidence, chronic suppressive therapy with acyclovir is beneficial in patients who have HAEM. (14)

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

1. Which of the following statements about HSV is true?
 - A. Anogenital herpes infections always are caused by HSV2.
 - B. Infection is more common in patients who have a higher socioeconomic status.
 - C. Most initial infections do not cause symptoms.
 - D. Orofacial infections should be treated with topical acyclovir.
 - E. Viral shedding lasts longer in reactivation than in an initial infection.
2. You are evaluating a 4-year-old girl who has had blisters around her mouth for 3 days. She has been immunized against VZV but recently was exposed to a child who has chickenpox. Physical examination reveals clusters of vesicles on an erythematous base around her lips. You wonder if this is a primary HSV infection or a mild VZV infection. Of the following, the test that is *least* likely to help you distinguish between these two infections is:
 - A. HSV and VZV antibody titers.
 - B. HSV DFA.
 - C. HSV PCR.
 - D. Tzanck smear.
 - E. Viral culture.
3. You are seeing a 1-day old boy in the newborn nursery because of a rash. He was born at term to a mother who had prenatal care and no history of STIs. He is sluggish at breastfeeding and appears ill. Physical examination reveals several vesicles on his scalp and face. You suspect neonatal herpes infection. Of the following, a true statement regarding this infant and his mother is that:
 - A. Acyclovir should be administered to the infant as soon as possible.
 - B. Administration of acyclovir to the mother during delivery could have prevented this infection.
 - C. Breastfeeding should be stopped to avoid additional spread of the infection.
 - D. His mother likely has a recent recurrence of a genital herpes infection.
 - E. His mother likely was infected with herpes in her first trimester.
4. Which of the following HSV infections is correctly matched with the appropriate treatment?
 - A. Genital herpes and topical acyclovir.
 - B. Gingivostomatitis and IV acyclovir.
 - C. Herpes gladiatorum and oral foscarnet.
 - D. Keratoconjunctivitis and topical vidarabine.
 - E. Neonatal herpes and oral acyclovir.

Inborn Errors of Metabolism:

Part 1: Overview

Paul A. Levy, MD*

Author Disclosure
Dr Levy did not disclose any 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. Recognize the signs and symptoms that are suggestive of an inborn error of metabolism.
2. Describe the characteristics of different classes of metabolic syndromes.
3. Formulate a logical diagnostic approach to determining which specific condition is present when an inborn error of metabolism is suspected.
4. Delineate the value and scope of newborn screening programs.
5. Be aware of treatment modalities for inborn errors of metabolism.

Introduction

As hospitalizations for traditional pediatric illnesses have declined during the last century, due primarily to improved treatment of infectious diseases, the contribution of other disorders has gained prominence. Biochemical genetics, with its various inherited metabolic disorders (inborn errors of metabolism), has become more important in the routine care of hospitalized pediatric patients. Newborn screening also is contributing to the increased awareness of inherited metabolic disorders. Only a few years ago, most states tested for only as many as eight disorders, generally including phenylketonuria, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, sickle cell disease, hypothyroidism, and congenital adrenal hyperplasia. Recent changes in technology have permitted an increase in the number of disorders tested. A national panel has recommended expanding the testing to 29 disorders, but many states already have begun to screen for more than 40 different disorders with the new technology of tandem mass spectrometry. This expanding list includes amino acid disorders, organic acid disorders, urea cycle diseases, and fatty acid oxidation defects. Some states are working to add lysosomal storage diseases and peroxisomal disorders to their newborn screening panels.

Pediatricians need to recognize and become familiar with these diseases not only to help with the diagnosis but also to help educate parents and advocate for patients. Some patients may fall ill with inherited metabolic disorders not currently detected by newborn screening; others may have conditions that were missed on their newborn screens. Affected children may present at a few days to a few months of age with lethargy or vomiting and be thought to have sepsis or shock. Other disorders may present at a later age with a more indolent picture of developmental delay or regression.

Attempts have been made at developing a rational framework for conceptualizing inherited metabolic diseases, but there is no one simple method of categorizing all of the inherited metabolic diseases with their many different presentations and various ages of onset.

This review is in two parts. The article that appears in print offers a simplified approach to diagnosis and a discussion of the presentation of and testing for many groups of inherited metabolic disorders. The second part appears online only and provides a more detailed discussion of the various groups of inherited metabolic disorders.

Abbreviations

CDG:	congenital disorders of glycosylation
GSD:	glycogen storage disease
KGDH:	alpha-ketoglutarate dehydrogenase
MPS:	mucopolysaccharidosis
MRI:	magnetic resonance imaging
OXPHOS:	oxidative phosphorylation
PCD:	pyruvate carboxylase deficiency
PDD:	pyruvate dehydrogenase deficiency

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Table 1. Inborn Errors of Metabolism Associated With an Acute Crisis

Diagnostic Clues		Suggested Disorders
Primary	Secondary	
Acidosis	± Hypoglycemia	Various organic acid disorders
	± Lactic acidosis	
	± Ketosis	
	± Elevated ammonia	
	Increased anion gap	
	Significant lactic acidosis	Mitochondrial disorders
	Normoglycemia	Pyruvate dehydrogenase deficiency
		Alpha-ketoglutarate dehydrogenase deficiency
		Pyruvate carboxylase deficiency
	Significant lactic acidosis	Glycogen storage type I
	Hypoglycemia	Fructose-1,6-bisphosphatase deficiency
	Normal anion gap	Renal tubular acidosis
	Normal lactate	
	No ketosis	
Hyperammonemia	Alkalosis or normal pH	Urea cycle disorders
	Normal lactate	
	Reye-like illness (hypoglycemia, elevated liver transaminases, normal ketones)	Fatty acid oxidation defects
	Acidosis	Various organic acid disorders
	± Lactic acidosis	
	± Ketosis	
	± Hypoglycemia	
	Increased anion gap	
Hypoglycemia	Acidosis	Various organic acid disorders
	± Ketosis	
	± Lactic acidosis	
	± Increased ammonia	
	Increased anion gap	
	Hepatomegaly	Glycogen storage disorders
	± Lactic acidosis	
	No ketosis	Hyperinsulinemia
	No acidosis	Fatty acid oxidation defects
	Normal lactic acid	
	Hyponatremia	Adrenal insufficiency
	Hypotension	
	Signs of liver failure	Tyrosinemia
		Glycogen storage disease type IV
		Galactosemia
		Niemann Pick type C

Approach to Diagnosis and Testing

In general, inherited metabolic disorders can be divided into two groups: disorders that can present with an acute crisis (Table 1), often with encephalopathy, and disorders that have a more chronic, indolent course (Table 2). Two authors have made significant contributions to help clinicians identify and diagnose inherited metabolic disorders. Jean Marie Saudubray (*The Molecular and Metabolic Bases of Inherited Disease*. 8th ed. New York, NY: McGraw Hill; 2001, updated online at www.ommbid.com) and JTR Clarke (*A Clinical Guide to Inherited Metabolic Diseases*. 2nd ed. New York, NY: Cambridge

University Press; 2002) have described frameworks for the evaluation of these diseases. This review provides a simplified overview, but readers are encouraged to consult these references for additional assistance in diagnosing inherited metabolic disorders.

Acute Presentation

Children who have inherited metabolic disorders almost always appear normal at birth because the metabolic intermediate that is responsible for the disorder frequently is a small molecule that can traverse the placenta and be eliminated by the mother's metabolism. Once the

Table 2. Findings Suggestive of a Chronic Metabolic Disorder**Neurologic**

Developmental delay (especially with regression), seizures (myoclonic or partial complex), seizures resistant to anticonvulsant therapy, deafness, blindness, stroke, or movement disorder (dystonia, chorea)

Liver

Hepatosplenomegaly, cholestasis, liver failure (\pm cirrhosis), hypoglycemia

Heart

Cardiomyopathy (dilated or hypertrophic), arrhythmias

Kidney

Enlarged kidneys with microcysts, renal failure, tubular dysfunction, generalized amino aciduria, hypophosphatemia, rickets

Muscle

Peripheral muscle weakness, myoglobinuria

Eye

Cataracts, corneal opacities, lens dislocation, retinal abnormalities (cherry red spots, retinitis pigmentosa), ophthalmoplegia, strabismus

Dysmorphic Features

Macrocephaly, high forehead, large anterior fontanelle, coarsened facial features, large jaw, small jaw, large ears, abnormal fat distribution

infant is born, symptoms begin to appear after a variable period of time (days, weeks, months, or rarely, years) as the metabolite accumulates.

An acute presentation is most common in infants and young children. Infants have a limited repertoire with which to respond to an overwhelming illness. Generally, they manifest poor feeding and lethargy. Trying to distinguish a routine childhood illness from an inherited metabolic disorder can be difficult. Even if there is vomiting, respiratory distress, and eventually encephalopathy (coma), such symptoms most commonly are attributed to infection and sepsis, not to an inherited metabolic disorder. Routine blood tests, cultures, and chest radiographs yield unremarkable results. An important clue that should stimulate the clinician to look further is the lack of improvement with standard therapy.

Organic acidemias, urea cycle defects, and some disorders of amino acid metabolism can result in acute

encephalopathy. An inherited metabolic disorder always should be considered in the differential diagnosis, especially if there are no associated risk factors for infection. Consideration of these disorders may require some diagnostic suspicion, but identifying them requires only a few laboratory tests.

When presented with a child who has acute encephalopathy, the clinician must determine the pH, lactate value, electrolyte concentrations, liver function, and glucose status of the patient. Ammonia should be measured for any ill child who has unexplained lethargy or vomiting. The presence of ketones in the urine also may be important. The results of such tests can help to diagnose an underlying inherited metabolic disorder.

Acidosis

The presence of acidosis ($\text{pH} < 7.30$, $\text{PCO}_2 < 30$ torr, and $\text{HCO}_3^- < 15$ mEq/L [15 mmol/L]) indicates significant disturbance of normal metabolism and may result from infection, dehydration, intoxication, or anoxia as well as from an inborn error of metabolism. Organic acid disorders present with acidosis due to the accumulation of acidic metabolites. Hypoglycemia, lactic acidosis, ketosis, and a mild to moderately elevated ammonia value also may be present, either individually or together. The presence or absence of these other findings may help distinguish among different organic acidemias.

If hypoglycemia is present with lactic acidosis but no significant ketosis, disorders of gluconeogenesis should be investigated. Significant lactic acidosis may suggest the possibility of an energy production disorder, either a mitochondrial defect of oxidative phosphorylation (OXPHOS), pyruvate dehydrogenase deficiency (PDD), α -ketoglutarate dehydrogenase (KGDH) deficiency, or pyruvate carboxylase deficiency (PCD). Finally, acidosis without the elevation of lactate or the presence of ketosis and a normal anion gap suggests renal tubular acidosis.

LACTIC ACIDOSIS. Lactic acidosis often results from hypoxia or poor perfusion, which may be caused by dehydration. Glycogen storage diseases, pyruvate metabolism defects (PDD, PCD, KGDH), fructose-1,6-bisphosphatase deficiency, and mitochondrial OXPHOS abnormalities increase lactic acid production directly; organic acid disorders may cause a secondary rise in lactate. In many hospitals, it is relatively simple to measure lactic acid on a blood gas determination. Such testing is optimal because it provides both the pH and the lactate values quickly. Determination of the lactic

acid value helps with the diagnosis of organic acidurias and glycogen storage diseases.

For other disorders, it may be beneficial to measure pyruvate, but this determination is more difficult because the blood must be drawn and placed immediately into a special tube. Generally, the result is not available immediately. An increased lactic acid value with a lactic acid-to-pyruvate ratio of less than 25 is normal, but the elevated lactic acid suggests a defect in pyruvate dehydrogenase or an enzyme of gluconeogenesis (fructose-1,6-bisphosphatase or glucose-6-phosphatase). An increased ratio (>30) suggests a deficiency of pyruvate carboxylase or KGDH or an OXPHOS defect. Determination of blood ketones (3-hydroxybutyrate and acetoacetic acid) helps to delineate the defect further. A ratio of 3-hydroxybutyrate-to-acetoacetic acid greater than 2:1 is suggestive of an OXPHOS defect.

KETOSIS. Ketosis is a normal physiologic response in some circumstances, but it is not normal when it is severe enough to cause acidosis. Neonates do not generate ketones well, so the presence of ketones in a newborn's urine is of concern. Many organic acidurias present with ketosis. Persistent ketosis with normal urine organic acids suggests a defect in one of two ketolytic enzymes.

HYPERAMMONEMIA. Ammonia values may be elevated in a number of disorders, including urea cycle defects, some organic acidemias, and fatty acid oxidation defects that may present with a Reye-like syndrome (vomiting, elevated liver transaminases, hyperammonemia, coma). The organic acid disorders can be distinguished by the presence of acidosis. Fatty acid oxidation defects generally create hypoglycemia, which the urea cycle defects do not.

HYPOGLYCEMIA. When hypoglycemia is an isolated finding, hyperinsulinism should be considered. Hypoglycemia also can be associated with liver failure, so both metabolic disorders (tyrosinemia, glycogen storage disease [GSD] type IV, galactosemia, and Niemann-Pick disease type C) as well as congenital malformations and acquired conditions should be ruled out. If the hypoglycemia is associated with hepatomegaly (\pm lactic acidosis), glycogen storage diseases (GSD I, III, VI, and IX) and fructose-1,6-bisphosphatase deficiency are likely. When acidosis or ketosis is present with hypoglycemia, the organic acidurias are a likely cause. Hypoglycemia without ketosis (beyond the newborn period) should prompt investigation for a fatty acid oxidation defect. Lastly, hypoglycemia with hyponatremia and hypotension may

be a presentation of adrenal insufficiency, especially in patients who have been receiving steroids chronically.

Treatment of Encephalopathy

Presentation of an infant or young child in an encephalopathic coma requires urgent treatment in an attempt to avert or mitigate neurologic sequelae and potential death from a treatable cause. Recognizing the possibility that an inborn error of metabolism may be responsible should prompt appropriate laboratory tests (ammonia, lactic acid, urine organic acids, plasma and urine amino acids, pH, glucose, liver function tests, pyruvate, acylcarnitine profile). The results of these tests may not be immediately available, but they should be completed in 48 to 72 hours. Treatment can begin before a definitive diagnosis is determined.

An elevated ammonia concentration without acidosis is presumed to be a urea cycle defect. Immediate arrangements for hemodialysis should be made and ammonia removal medications (sodium benzoate and sodium phenylacetate) and arginine administered. All protein intake should be halted if a urea cycle defect or a disorder related to protein "intolerance" such as an organic acidemia is suspected. Such protein deprivation cannot be undertaken without providing appropriate caloric intake from carbohydrate (10% glucose) and an intravenous fat emulsion. If the caloric intake is not sufficient, catabolism of the patient's protein occurs, raising ammonia concentrations in a urea cycle disorder or presenting substrate for the organic acidurias.

A number of inherited metabolic disorders respond to large ("mega") doses of the cofactors of their respective enzymes. Presumptively, a "cocktail" of such cofactors can be started for a possible inherited metabolic disorder. Vitamin B₁₂ (hydroxycobalamin) (1 mg/day intramuscularly), thiamine (50 mg orally BID), biotin (10 mg orally BID), riboflavin (50 mg orally BID), folic acid (10 mg orally BID), and carnitine (100 mg/kg per day orally divided QID) have been found to be effective for a number of disorders and should be administered. Patients who experience hypoglycemia should be given glucose to maintain normal plasma concentrations. Treatment can be tailored as the results of testing become available and a diagnosis is made.

Chronic Disorders

The second group of metabolic disorders is characterized by a more chronic course. They are difficult to recognize and diagnose because their onset may be from birth to adulthood and they have myriad signs and symptoms. The presence of some clinical findings helps to organize

the group into more manageable subgroups. The first and largest subgroup is disorders that create neurologic abnormalities. Involvement of a specific organ system may suggest a specific inherited metabolic disorder and comprise the second subgroup. The third subgroup is defined by the presence of dysmorphic features, which although not common to many inherited metabolic disorders, can be a helpful distinguishing feature.

Neurologic

Neurologic findings may include developmental or psychomotor delay, seizures, movement disorders, deafness, and blindness. Psychomotor or developmental delay is the most common clinical finding of inherited metabolic disorders. Not all children who exhibit developmental delay, however, have inherited metabolic disorders. Developmental delay due to an inherited metabolic disorder usually is global (rather than an isolated delay of speech, for example) and shows loss of milestones (regression) over time as the disease progresses.

Seizures, if they occur, are of various types, with electroencephalographic findings that may be difficult to classify into a specific seizure syndrome. Seizures (often myoclonic or partial complex) that are resistant to anticonvulsant therapy may suggest an underlying inherited metabolic disorder.

Movement disorders associated with inherited metabolic disorders include dystonias (abnormal muscle contractions that result in abnormal postures and involuntary torsional movements) and choreas (involuntary movements that can be athetotic and involve twisting or torsional movements).

Although there may be some overlap, involvement of either gray matter or white matter may help in narrowing the differential diagnosis of the underlying disorder. Disorders involving the cerebral gray matter tend to occur early in life. In addition to developmental delay, patients who have these conditions may exhibit seizures, a movement disorder (chorea or dystonia), hearing loss, or blindness (cortical or due to optic atrophy). Magnetic resonance imaging (MRI) findings may show only some cerebral atrophy or be read as normal. Neuronal lysosomal storage diseases can be considered in such patients as well as some of the mitochondrial disorders.

Disorders involving the cerebral white matter generally have abnormalities of tone (hypotonia or hypertonia) and motor difficulties (sometimes delayed or loss of motor milestones). This group includes the leukodystrophies, which, by definition, have abnormal white matter, and Canavan disease, Alexander disease, and some of the lysosomal storage disorders.

Some inherited metabolic disorders may result in neuronal migration defects. These conditions include peroxisomal disorders and some congenital disorders of glycosylation.

Stroke, an unusual finding in children, should suggest homocystinuria and the mitochondrial disorder MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). Fabry disease and some forms of congenital disorders of glycosylation (CDG) also have been associated with stroke.

Other Specific Organ System Involvement

LIVER OR SPLEEN. Liver involvement may lead to hypoglycemia, cholestasis, or liver failure with cirrhosis. Disorders that lead to cirrhosis include tyrosinemia, classic galactosemia, hereditary fructose intolerance, the Zellweger spectrum of peroxisomal disorders, CDG, alpha-1-antitrypsin deficiency, Wilson disease, and mitochondrial disorders. Hypoglycemia may result from a GSD or a fatty acid oxidation defect as well as some organic acidurias. Lysosomal storage diseases, especially the mucopolysaccharidoses (MPSs), are characterized by hepatosplenomegaly and also present with dysmorphic (coarsened) features, intellectual disability, and short stature.

HEART. Some fatty acid oxidation defects may present with severe cardiomyopathy. Other disorders that have significant cardiac symptoms include carnitine transport disorders, Pompe disease (GSD type II), Fabry disease, G_{M1} gangliosidosis, CDG, and some mitochondrial diseases.

KIDNEY. Glutaric aciduria type II may cause enlarged kidneys that contain small microcysts and are detected at birth. Galactosemia and hereditary fructose intolerance with chronic exposure to fructose lead to proximal tubule dysfunction and kidney failure if left untreated. Tyrosinemia type I generally manifests tubular dysfunction, which results in hypophosphatemia and rickets. Cystinosis is associated with decreased glomerular function leading to end-stage renal failure. Fanconi syndrome (aminoaciduria) also may be caused by some mitochondrial diseases.

MUSCLE. Peripheral muscle weakness is characteristic of the muscle forms of GSD, generally appearing in older children and sometimes accompanied by myoglobinuria. Mitochondrial disease may cause muscle weakness with or without persistent lactic acidosis.

EYE. Ocular findings often provide a clue to an underlying inborn metabolic disorder. The presence of cataracts may suggest galactosemia, peroxisomal disorders, Lowe syndrome, alpha-mannosidosis, galactokinase deficiency, mitochondrial respiratory chain disorders, sialidosis, lysinuric protein intolerance, Sjögren-Larsson syndrome, and Wilson disease. In adults, patients who have Fabry disease or homocystinuria and carriers for both Lowe syndrome and galactosemia (galactose-1-phosphate uridylyltransferase deficiency and uridine diphosphate galactose-4-epimerase) also may develop cataracts.

Corneal abnormalities such as opacities can be seen in MPS I and VI, Wilson disease, galactosialidosis, cystinosis, Fabry disease, and tyrosinemia (ocular form). Homocystinuria and Marfan syndrome are associated with lens dislocation, as are molybdenum cofactor deficiency, sulfite oxidase deficiency, contractural arachnodactyly, and Marshall syndrome. Cherry red spots are found in a number of lysosomal storage diseases due to the accumulation of storage material in the retina, which causes paleness but a normal-appearing fovea, resulting in a central “spot.” This finding is associated with Tay-Sachs disease (G_{M2} gangliosidosis), G_{M1} gangliosidosis, sialidosis, Niemann-Pick disease, Farber disease, galactosialidosis, and metachromatic leukodystrophy.

Mitochondrial disease (Leigh syndrome, Kearns-Sayre syndrome), chronic progressive external ophthalmoplegia, and neurogenic weakness ataxia retinitis pigmentosa may be associated with retinitis pigmentosa as well as with weakness of the extraocular muscles leading to ophthalmoplegia. Other inherited metabolic disorders associated with retinitis pigmentosa include congenital disorders of glycosylation, ceroid lipofuscinoses, and peroxisomal disorders.

SKIN. Biotinidase deficiency often presents with alopecia and a rash (usually eczematike). Angiokeratomata characteristically are seen in Fabry disease, but also can be seen in fucosidosis, beta-mannosidosis, galactosialidosis, and aspartylglucosaminuria. Menkes syndrome is known for hair abnormalities (soft, pale, brittle, and wiry), but patients afflicted with arginosuccinic aciduria and citrullinemia also may have brittle hair.

Farber lipogranulomatosis (a sphingolipidosis) has unique periarticular subcutaneous nodules and also is characterized by joint swelling and contractures.

DYSMORPHIC FEATURES. Although not typical of most inherited metabolic disorders, dysmorphic features

can be a helpful diagnostic clue. The largest group of disorders associated with dysmorphic features is the lysosomal storage diseases. MPSs are the most identifiable members of this group and present with coarsened facial features, hepatosplenomegaly, and short stature. Other lysosomal disorders that present with dysmorphic features include some of the oligosaccharidoses (mannosidosis, galactosialidosis, aspartylglucosaminuria, sialidosis, and I-cell disease), which can involve features similar to those of the MPS disorders. G_{M1} gangliosidosis (a sphingolipidosis) also presents with MPS-like facial features. Farber lipogranulomatosis presents with dysmorphic features and characteristic periarticular subcutaneous nodules.

Only a few disorders present at birth or soon after with dysmorphic features: some of the lysosomal storage disorders, Sly syndrome, sialidosis, galactosialidosis, G_{M1} gangliosidosis, and Krabbe disease, as well as Pompe disease, which is a lysosomal disorder, although usually included with the GSDs. Peroxisomal disorders generally are associated with dysmorphic features characterized by the Zellweger spectrum (high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia). Finally, many of the CDG exhibit dysmorphic features (large ears, strabismus, abnormal fat distribution).

Evaluation

Evaluation for a possible inherited metabolic disorder in the chronic group begins with a developmental assessment and history. If an inherited metabolic disorder is suspected, a fairly extensive initial screen includes MRI of the brain; a skeletal survey; testing for plasma amino acids, urine organic acids, urinary mucopolysaccharides, and oligosaccharides; transferrin electrophoresis; measuring very long-chain fatty acids, pH, lactate, and ammonia; verifying results of the newborn screen; and obtaining an acylcarnitine profile and an ophthalmologic examination.

The MRI should help distinguish gray and white matter involvement as well as cerebellar hypoplasia (CDG) and neuronal migration defects (CDG and peroxisomal disorders). A skeletal survey may uncover evidence of dysostosis multiplex (lysosomal storage diseases). Urine testing for mucopolysaccharides and oligosaccharides may uncover many of the large group of lysosomal storage disorders. Measuring plasma amino

acids and urine organic acids is a good screen for disorders in these groups.

Transferrin electrophoresis helps with CDG, which are N-linked glycan synthesis disorders. Peroxisomal disorders can be screened for by measuring very long-chain fatty acids and phytanic acid. A pH and lactate measurement may reveal longstanding acidosis and elevated lactate values. Ammonia concentrations may be elevated with enzyme deficiencies of the urea cycle or some organic acid disorders. An acylcarnitine profile, similar to tandem mass spectrometry testing for newborn screens, can assist in the detection of fatty acid oxidation defects, carnitine transport defects, amino acid disorders, and organic acid disorders.

Results of the initial assessment (history and physical examination) can help to guide the evaluation, and some of these tests may be omitted. Positive results from such testing may lead to additional investigation and confirmatory testing by either an enzyme assay or DNA testing.

EDITOR'S NOTE. The second part of this article, which is published in the online edition of this issue, is a comprehensive overview of specific inborn errors of metabolism. Most readers will use this material as a reference resource. All readers are urged to familiarize themselves with this second portion of the article, which reflects a prodigious effort on the part of Dr Levy.

PIR Quiz

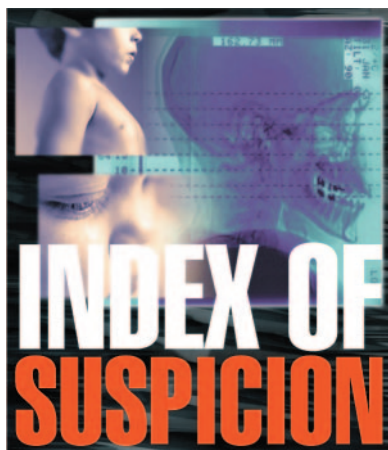
Quiz also available online at pedsinreview.aappublications.org.

5. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. Laboratory evaluation reveals a normal complete blood count; differential count; pH; and serum electrolytes, glucose, and lactate. Serum ammonia concentrations are high and urine ketones are absent. Of the following, the *most* likely explanation is:
 - A. Fatty acid oxidation defect.
 - B. Organic acidemia.
 - C. Renal tubular acidosis.
 - D. Sepsis.
 - E. Urea cycle defect.
6. On the second day after birth, an initially vigorous term infant begins to feed poorly, develops tachypnea, and becomes increasingly less responsive to stimulation. No other abnormal findings are detected on physical examination. Chest radiograph appears normal. The complete blood count and differential count are normal. The pH is low, serum ammonia value is high, sodium and chloride values are normal, potassium is elevated, bicarbonate is low, serum glucose is low, and serum lactate is slightly elevated. Ketones are present in the urine. Of the following, the *most* likely explanation is:
 - A. Fatty acid oxidation defect.
 - B. Organic acidemia.
 - C. Renal tubular acidosis.
 - D. Sepsis.
 - E. Urea cycle defect.

7. A previously healthy 2-month-old girl rapidly becomes comatose shortly after the onset of an apparent upper respiratory tract infection. Aside from clear nasal discharge and coma, findings on her physical examination are unremarkable. Chest radiography appears normal. Laboratory findings include a normal complete blood count and differential count, pH, serum electrolytes, and serum lactate. Serum ammonia values are high and serum glucose is low. There are no ketones in the urine. Of the following, the *most* likely explanation is:
 - A. Fatty acid oxidation defect.
 - B. Organic acidemia.
 - C. Renal tubular acidosis.
 - D. Sepsis.
 - E. Urea cycle defect.
8. A 12-month-old boy who has had progressive loss of developmental milestones over the past 6 months is found to have a cherry red spot on examination of each retina. He *most* likely suffers from a disorder of:
 - A. Glycoprotein synthesis.
 - B. Glycosylation.
 - C. Lysosomes.
 - D. Mitochondria.
 - E. Peroxisomes.
9. Physical examination of a newborn reveals a high forehead, flat occiput, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, and micrognathia. The infant *most* likely has a disorder of:
 - A. Amino acid metabolism.
 - B. Fatty acid oxidation.
 - C. Glycogenolysis.
 - D. Lysosomes.
 - E. Peroxisomes.

Correction

In the article “Adolescent Immunizations” in the February 2009 issue (*Pediatr Rev.* 2009;30:47–56), in Table 1, “group B *Streptococcus* (GBS)” is in error. The correct phrase is “Guillain-Barré syndrome (GBS)” and applies to both places where “GBS” is printed in that table. In addition, on page 55 of the article, the last sentence in the first paragraph of the section headed “Polio” should read: “Poliovirus, a member of the enterovirus family, perhaps is best known for causing a rapid onset of asymmetric acute flaccid paralysis with areflexia.”



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 Mian, Becton, Blackall, James, Berman, Turner, Givner, and Shetty and Mr Owusu 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.

Case 1 Presentation

A 16-month-old boy had been diagnosed with B-cell acute lymphoblastic leukemia (ALL). Past medical and birth histories were unremarkable. Over the past 48 hours, he received and tolerated a slow transfusion of packed red blood cells for an Hgb concentration of 4.9 g/dL (49 g/L). Currently, he is receiving maintenance intravenous hydration. Physical examination shows no evidence of distress. His temperature is 97.5°F (36.4°C), respirations are 24 breaths/min, heart rate is 126 beats/min, blood pressure is 95/64 mm Hg, and oxygen saturation is 98% on room air. His chest is clear to auscultation, with normal heart sounds. Abdominal examination shows mild hepatosplenomegaly. He has scattered petechiae. Current laboratory results are: WBC count of $14.8 \times 10^3/\text{mcL}$ ($14.8 \times 10^9/\text{L}$), Hgb of 10.4 g/dL (104 g/L), Hct of 28.9% (0.29), and platelet count of $48 \times 10^3/\text{mcL}$ ($48 \times 10^9/\text{L}$). The values for serum electrolytes, BUN, creatinine, liver enzymes, and uric acid as well as results of coagulation studies are within normal limits. Chest radiography reveals normal findings. Prior to surgery for central line placement, he receives 1 unit of irradiated, leukocyte-reduced platelets.

A central line is placed without difficulty. Within 2 hours of the platelet transfusion, he experiences acute cardiorespiratory deterioration (heart rate 165 beats/min, blood pressure 65/42 mm Hg, respiratory rate 48 breaths/min, oxygen saturation 78% on room air, and temperature 99°F [37.2°C]). Examination reveals symmetrically decreased breath sounds and diffuse crackles bilaterally, with normal heart sounds and capillary refill. Repeat radiography shows extensive “diffuse bilateral infiltrates consistent with pulmonary

edema.” He is intubated and transferred to the intensive care unit. Additional evaluations reveal the diagnosis.

Case 2 Presentation

A 13-month-old boy presents with a history of fever for 2 days and non-bloody diarrhea for 2 weeks. Other family members also report diarrhea over the past 2 weeks. He has been healthy, except for a 4-month history of easy bruising and a recent history of oral thrush. He is not taking any medications.

On physical examination, his temperature is 102.9°F (39.4°C) and other vital signs are normal. He appears ill but not toxic. He has multiple petechiae and ecchymoses all over his body, white plaques on the oral mucosa, and bilateral anterior cervical lymphadenopathy. The remaining findings of his physical examination are normal. Initial laboratory tests show a WBC count of $2.3 \times 10^3/\text{mcL}$ ($2.3 \times 10^9/\text{L}$), with 62% bands, 22% neutrophils, 18% lymphocytes, and 5% monocytes; Hgb of 8.8 g/dL (88 g/L); and platelet count of $11 \times 10^3/\text{mcL}$ ($11 \times 10^9/\text{L}$). Stool studies yield negative results.

He is started on empiric cefepime and fluconazole but soon becomes more irritable and develops nuchal rigidity as well as bilateral sixth cranial nerve palsy. A CT scan of his head shows mild ventriculomegaly. A lumbar puncture is performed, and analysis of the CSF shows glucose of 37 mg/dL, protein of 300 mg/dL, 420 red blood cells/mm³ and 1,319 WBCs/mm³. Blood and CSF cultures subsequently grow *Listeria monocytogenes*. Antibiotics are changed to ampicillin and gentamicin. An intraventricular catheter (IVC) is placed to relieve the increased intracranial pressure. Addi-

tional studies reveal why this patient contracted this unusual infection.

Case 3 Presentation

A 17-year-old Hispanic boy presents to the ED with a 5-day history of fever and severe abdominal pain. The pain is intermittent and localized to the epigastrium and right flank. He denies vomiting, diarrhea, and bloody stools but complains of loss of appetite, weight loss, constipation, mild headache, and a dry cough over

the past 2 weeks. The past medical history is unremarkable. There is no history of recent international travel or exposure to animals.

Physical examination reveals an obese, alert adolescent whose temperature is 101.2°F (38.5°C), heart rate is 114 beats/min, respiratory rate is 24 breaths/min, blood pressure is 118/68 mm Hg, and oxygen saturation is 97% on room air. He has right upper quadrant abdominal tenderness, but his liver and spleen are not enlarged. Results of the rest of the examination are unremarkable.

Laboratory studies show a WBC count of $24.1 \times 10^3/\text{mcL}$ ($24.1 \times 10^9/\text{L}$) with 68% neutrophils, 13% bands, 13% monocytes, and 6% lymphocytes; Hgb of 14.3 g/dL (143 g/L); and platelet count of $334 \times 10^3/\text{mcL}$ ($334 \times 10^9/\text{L}$). The ESR is 62 mm/hr and C-reactive protein is 390.1 mg/L (39.0 mg/dL). Measurements of electrolytes, amylase, and lipase as well as renal function tests, liver function tests, and urinalysis are normal. ALT is mildly elevated at 44 U/L (normal, 10 to 40 U/L). Serologic tests for HIV and hepatitis A, B, and C are negative. Blood and stool cultures are negative for bacteria. Fecal ova and parasite examinations are negative. A purified protein derivative skin test is positive. Chest radiography shows increased interstitial markings with patchy opacities in the right middle lobe and both lower lobes.

Imaging of the abdomen leads to an additional test that reveals the diagnosis.

Case 1 Discussion

Immediately after the onset of respiratory symptoms, the serum electrolytes, BUN, and creatinine values were normal. His intake and output over the previous 24 hours were

matched, and he had appropriately colored urine output. ECG was read as normal, and echocardiography showed normal anatomy with normal cardiac function and no evidence of left atrial hypertension. There was no obvious evidence of circulatory overload, underlying infection, bacterial contamination of the donor unit, or acute hemolytic or anaphylactic transfusion reactions. Transfusion-related acute lung injury (TRALI) was diagnosed.

Clinical Course and Management

The patient was placed on mechanical ventilation for 2 days and started on prednisone for his induction chemotherapy protocol for ALL. He subsequently was extubated, received supportive management, and was discharged from the hospital on day 7.

The Condition

TRALI is a diagnosis of exclusion in a patient who presents with symptoms of acute respiratory distress, such as hypoxemia, tachycardia, or tachypnea, with bilateral diffuse infiltrates on frontal chest radiograph and no evidence of left atrial hypertension, noncardiogenic pulmonary edema, or pre-existing acute lung injury (ALI). The presentation occurs classically within 6 hours of receiving any blood product. In TRALI, a temporal relationship to an alternate risk factor for ALI, such as transfusion-associated circulatory overload (TACO), does not exist. TRALI is the leading cause of death in transfusion medicine, having an estimated mortality rate of 10%.

TRALI and acute respiratory distress syndrome (ARDS) have many common clinical features, but there are notable clinical differences. In TRALI, most patients show clinical, physiologic, and radiographic resolu-

Abbreviations

AA:	aplastic anemia
ALA:	amebic liver abscess
ALL:	acute lymphoblastic leukemia
ALI:	acute lung injury
ALT:	alanine aminotransferase
ARDS:	acute respiratory distress syndrome
ATG:	antithymocyte globulin
BUN:	blood urea nitrogen
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
EBV:	Epstein-Barr virus
ECG:	electrocardiography
ED:	emergency department
ESR:	erythrocyte sedimentation rate
Hct:	hematocrit
Hgb:	hemoglobin
HHV:	human herpesvirus
HIV:	human immunodeficiency virus
HLA:	human leukocyte antigen
HNA:	human neutrophil antigen
IVC:	intraventricular catheter
PCR:	polymerase chain reaction
TACO:	transfusion-associated circulatory overload
TRALI:	transfusion-related acute lung injury
WBC:	white blood cell

tion of symptoms within 2 to 3 days of the onset of the condition. Moreover, their underlying pulmonary injury is reversible, and there are no long-term residual pulmonary function deficits.

All blood components have been implicated in TRALI, including red blood cells, platelets, plasma, cryoprecipitate, granulocytes, stem cells, immune globulin concentrates, and autologous red cells. The estimated incidence is 1 in 5,000 to 1 in 25,000 transfusions. There is consensus that many cases are not reported and mild cases may be unrecognized. Because there is no specific diagnostic test, the 2004 consensus panel on TRALI developed clinical guidelines (Table) to enhance awareness and improve reporting to local transfusion services. (1)

Table. Criteria for Diagnosing TRALI

TRALI Criteria

Acute lung injury (ALI)

- Acute onset
- Hypoxemia
 - $\text{PaO}_2/\text{FiO}_2 < 300$ or $\text{SpO}_2 < 90\%$ on room air
- Bilateral infiltrates on frontal chest radiography
- No evidence of left atrial hypertension (ie, circulatory overload)

No pre-existing ALI before transfusion

Occurs during or within 6 hours of transfusion

No temporal relationship to an alternate risk factor for ALI

Possible TRALI

ALI

No pre-existing ALI before transfusion

During or within 6 hours of transfusion

A clear temporal relationship to an alternate risk for ALI

The pathogenesis of TRALI is understood incompletely, but there are two major schools of thought. The first hypothesis involves the infusion of a blood product that contains an antibody against the human leukocyte antigen (HLA) or human neutrophil antigen (HNA) for which the recipient has the cognate antigen. This situation leads to leukoagglutination, congestion of the pulmonary vasculature, neutrophil degranulation, and subsequently, endothelial injury and capillary leak. The second hypothesized mechanism is a “two-hit” model in which the first hit is the underlying clinical condition that leads to the elaboration of cytokines, which causes pulmonary endothelial activation resulting in pulmonary sequestration of neutrophils. The second hit is the infusion of the blood product that contains a biologically active lipid (lysophosphatidylcholine) that causes neutrophils to degranulate, resulting in endothelial damage and subsequent capillary leak.

The laboratory evaluation of TRALI and donor management is expensive and involves donor testing for antibodies against classes I and II HLA and HNA from a residual volume of the transfused blood component or a fresh blood specimen obtained from the blood donor. HLA typing on the recipient also is performed. A donor is regarded as “implicated” in TRALI if he or she is found to have HLA class I or II antibodies or HNA antibodies that have specificity for the recipient’s WBCs. Once a donor has been implicated, the consensus panel recommends that the he or she be deferred permanently from donation, which is not applied universally because of a smaller donor pool. This recommendation is based on instances in which donors who had specific antibodies

have been implicated in TRALI reactions involving multiple recipients.

Differential Diagnosis

For patients experiencing acute pulmonary insufficiency following blood product transfusion, the differential diagnosis includes TACO, which may present as respiratory distress, hypertension, and tachycardia when there is a mismatch of intake and output. Patients who have TACO show rapid resolution and improvement with aggressive diuresis. Anaphylactic transfusion reactions develop very rapidly and commonly present with erythema, urticaria, bronchospasm, and laryngeal edema rather than the noncardiogenic pulmonary edema seen in TRALI. Bacterial contamination of the blood product, leading to sepsis, presents as a sudden high fever, with or without rigors or chills, and cardiovascular collapse. Among these patients, respiratory symptoms usually are not prominent. Acute hemolytic transfusion reactions may present with signs of intravascular hemolysis that typically would not be confused with TRALI. ARDS, due to causes such as toxins or infections, also may present as respiratory distress and needs to be considered in the appropriate clinical setting.

Treatment

Early recognition and prompt respiratory and hemodynamic supportive measures are the hallmarks of management. Almost all patients require supplemental oxygen. In severe hypoxemia, intubation and mechanical ventilation with relatively high positive end-expiratory pressure are necessary. Inotropes may be needed to support the hemodynamic status. Although patients may not experience volume overload, diuresis commonly is undertaken. The role of steroids is somewhat controversial, but many

clinicians choose to administer a short course. Intravenous immunoglobulin administration does not alter the clinical course or outcome and is not indicated routinely. With appropriate timely management, most patients who have TRALI recover completely within 96 hours. Delay in management may lead to unnecessarily prolonged hospitalization as well as additional morbidity and mortality. Because anti-HLA antibodies may be implicated in TRALI and because multiparous women often have multiple HLA antibodies, some have recommended that such individuals be screened for HLA antibodies or excluded as donors of fresh frozen plasma and other blood products containing plasma.

Lessons for the Clinician

TRALI is a diagnosis of exclusion and should be considered in all patients who develop acute cardiorespiratory symptoms within 6 hours of blood product transfusion. Clinical criteria, developed by a TRALI consensus panel, serve as a useful diagnostic tool. Timely recognition and prompt supportive management are critical to decreasing mortality. Appropriate reporting and donor management also are critical and may serve to enhance understanding of the pathogenesis of TRALI. (*Amir Mian, MD, David Becton, MD, Douglas P. Blackall, MD, University of Arkansas for Medical Sciences, Little Rock, Ark.*)

Reference

1. Kleinman S, Caulfield T, Chan P, et al. Towards an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion*. 2004;44:1774–1789

Case 2 Discussion

The occurrence of listeriosis at an atypical age in the setting of pancytopenia warranted additional investigation. T- and B-lymphocyte enumeration showed CD4 lymphopenia with 4% CD4 cells (normal, 31% to 54%) and an absolute CD4 count of $0.18 \times 10^9/L$ (normal, 1 to $4.6 \times 10^9/L$). Results of human immunodeficiency virus (HIV) enzyme immunoassay and HIV DNA polymerase chain reaction (PCR) were negative. Immunoglobulin values and specific antibody titers were within normal limits. A bone marrow aspiration and biopsy revealed hypocellularity with an increased number of histiocytes demonstrating hemophagocytosis, but there were no blast cells, dysplasia, or fibrosis.

Hemophagocytic lymphohistiocytosis was considered, but several key diagnostic features such as splenomegaly, hypofibrinogenemia, and hypertriglyceridemia were absent. Investigation into possible viral causes detected Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6) by PCR. The patient was treated supportively with packed red blood cell and platelet transfusions, as well as with granulocyte-colony stimulating factor injections. The IVC was removed after 3 days. He completed a 21-day course of ampicillin and gentamicin. Although he improved clinically, his cell counts failed to improve. Therefore, a repeat bone marrow aspiration and biopsy were performed, which showed aplastic anemia. The patient did not have an HLA-matched bone marrow donor, so he underwent immunosuppressive therapy with cyclosporine and antithymocyte globulin (ATG). He responded well, and a follow-up bone marrow aspiration 1 year later yielded normal results.

The Presenting Condition

Listeria monocytogenes is a facultatively anaerobic gram-positive bacillus that most commonly causes illnesses in infants younger than 2 months of age, pregnant women, the elderly, and persons who have impaired cell-mediated immunity. Bacteremia and meningitis are the two most common invasive infections caused by *Listeria*. In contrast to other forms of bacterial meningitis, *Listeria* infection may involve the brain parenchyma and has been associated with encephalitis and brain abscesses. *Listeria* also causes a self-limited febrile gastroenteritis. Foods such as soft cheeses, deli meats, raw vegetables, unpasteurized milk, and poultry are common sources of *Listeria*.

Gastrointestinal *Listeria* infections do not require treatment, but ampicillin is the antibiotic of choice for invasive listeriosis. Gentamicin may be added for synergistic effect. Trimethoprim-sulfamethoxazole is an alternative for penicillin-allergic patients. CNS infections should be treated for at least 21 days; bacteremia without meningitis may be treated with a shorter course.

The Underlying Condition

Aplastic anemia (AA) is defined as pancytopenia that has an underlying hypocellular bone marrow. Its annual incidence is estimated to be 2 to 4 cases per 1 million, with a peak in adolescents, young adults, and the elderly. AA has inherited, acquired, and idiopathic forms. Examples of inherited AA forms are Fanconi anemia and Shwachman-Diamond syndrome. Acquired AA may be due to irradiation, drugs (nonsteroidal anti-inflammatory drugs, cancer chemotherapeutic agents, chloramphenicol, psychotropic agents), chemical toxins (benzene), viruses (EBV, HHV-6, cytomegalovirus, herpes simplex

virus, parvovirus, HIV, hepatitis virus), immune dysfunction (hypogammaglobulinemia, graft versus host disease, defects in cell-mediated immunity), and pregnancy. Myelodysplastic syndromes, malignancy, and other infections (babesiosis, ehrlichiosis, and tuberculosis) must be differentiated from AA as causes of pancytopenia and hypocellular bone marrow.

The most common presentations of AA are symptoms related to low peripheral blood cell counts. Thrombocytopenia may present with easy bruising, petechiae, gingival bleeding, and epistaxis. Anemia may cause fatigue, lightheadedness, and dyspnea on exertion. Neutropenia presents with several bacterial or fungal infections.

AA occasionally may be associated with a hemophagocytic syndrome, usually of viral origin, which was the case in this patient. Hemophagocytosis results when erythrocytes, leukocytes, platelets, and their precursors undergo phagocytosis by macrophages in the bone marrow, a process that is believed to be mediated by overproduction of cytokines. (1) Hemophagocytic syndromes cause pancytopenia, which develops during the convalescent phase of many viral infections, most commonly with the herpesviruses, but also with parvovirus and HIV. Hemophagocytosis also can be caused by bacterial, parasitic, and fungal infections.

Clues in the history, physical examination, and laboratory data may point toward AA, but the diagnosis cannot be made without examination of the bone marrow and the finding of hypocellularity. After being diagnosed, AA should be considered a medical emergency, due to the potential complications of pancytopenia. Definitive treatment is with allogeneic hematopoietic stem cell

transplantation, ideally from an HLA-matched sibling donor. Immunosuppressive therapy with cyclosporine or ATG is the treatment of choice if transplantation is not an option. Management also consists of correcting any significant cytopenias. Opportunistic infections should be treated aggressively, and prophylaxis should be provided until leukopenia resolves.

The prognosis of AA is correlated directly with the severity of blood cell count depression at presentation, especially the degree of neutropenia. Untreated severe AA almost invariably is fatal, whereas more moderate AA has a very good long-term survival if treated. Some mild forms of AA are self-limited and do not require treatment.

Lessons for the Clinician

In the pediatric population, listeriosis after 2 months of age is unusual and should raise suspicion for an underlying deficiency in cell-mediated immunity. AA occasionally can be a cause of such an immunodeficiency due to profound leukopenia. In the setting of pancytopenia, bone mar-

row aspiration is necessary to distinguish among AA, hemophagocytic syndrome, malignancy, myelodysplastic syndromes, and viral suppression. If AA of any cause is found, definitive treatment with allogeneic stem cell transplantation should be undertaken as soon as possible. Immunosuppressive therapy is needed if a matching family or unrelated donor is not available. (Scott H. James, MD, University of Alabama at Birmingham, Birmingham, Ala; David M. Berman, DO, All Children's Hospital, St. Petersburg, Fla.)

Reference

1. Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with hemophagocytic syndrome. *Lancet Infect Dis.* 2007;7:814–822

Case 3 Discussion

Contrast-enhanced CT scan of the abdomen (Figure) revealed a 5.7×7.2-cm peripherally enhancing, low-density lesion in the posterior right hepatic lobe, which was most suggestive of hepatic abscess. The differential diagnosis includes pyo-

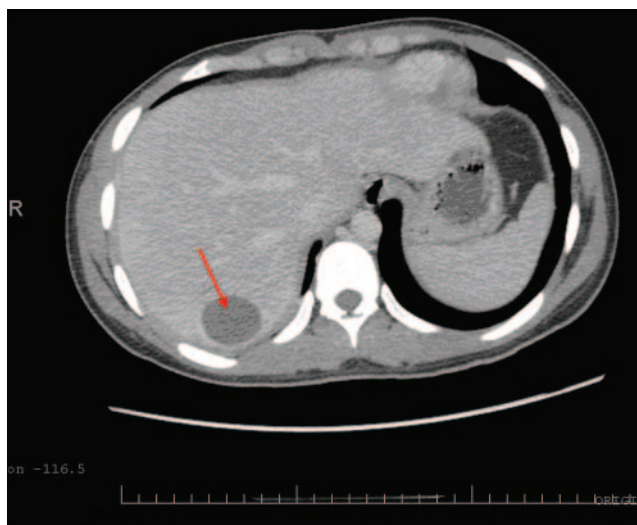


Figure. CT scan of the abdomen showing peripherally enhancing low-density lesion in the posterior aspect of the right hepatic lobe.

genic and amebic liver abscesses (ALA). Distinguishing between them is critical because the treatment and prognosis differ. The microbiology of pyogenic abscesses is highly variable because infection can occur by hematogenous seeding or by contiguous spread from an intra-abdominal source. Leading causative organisms include *Staphylococcus aureus*, *Salmonella*, *Klebsiella pneumoniae*, *Escherichia coli*, and anaerobes. Among the other unusual pathogens are *Bartonella henselae*, *Nocardia asteroides*, *Yersinia pseudotuberculosis*, and *Y enterocolitica*. Nonpyogenic liver abscesses are rare in developed countries. Organisms causing nonpyogenic liver abscesses include amoeba, mycobacteria, *Echinococcus*, and fungi.

Clinical Course

The patient was admitted to the pediatric infectious disease service and was started on intravenous metronidazole, clindamycin, and ceftriaxone to treat both amebic and pyogenic infection. Percutaneous drainage of the abscess under fluoroscopy and ultrasonographic guidance was carried out for diagnostic purposes. Culture of abscess fluid was negative for bacteria and fungi. Serologic testing for *Entamoeba histolytica* antibodies was strongly positive (immunoglobulin G, 7.32; normal, <0.9). On the third day of hospitalization, the boy became afebrile and improved clinically. A repeat abdominal CT scan on day 6 of hospitalization showed significant decrease in the size of the abscess cavity. He received a 7-day course of intravenous metronidazole and was discharged to complete a 20-day course of iodoquinol at home. Although this patient had not traveled, he may have acquired this amebic infection from a family member who visited him from Mex-

ico several months prior to presentation.

Amebic Liver Abscess (ALA)

Amebiasis, caused by the intestinal protozoal parasite *Entamoeba histolytica*, remains a global health problem, infecting about 50 million people and resulting in 40,000 to 100,000 deaths per year. The prevalence may be as high as 50% in tropical and subtropical countries where overcrowding and poor sanitation are common. In the United States, *E histolytica* infection is seen most commonly in immigrants from developing countries, long-term travelers to endemic areas (most frequently Mexico or Southeast Asia), institutionalized individuals, and men who have sex with men. In 1993, the previously known species *E histolytica* was reclassified into two genetically and biochemically distinct but morphologically identical species: the pathogenic *E histolytica* and the nonpathogenic commensal *E dispar*.

Pathogenesis

E histolytica is transmitted via the fecal-oral route. The ingested amebic cysts are resistant to gastric acid and undergo excystation in the small intestine, releasing mobile trophozoites that infect the colon. The trophozoites adhere to the colonic epithelium, where pathogenic strains produce ulcerative lesions, resulting in colitis. Asymptomatic cyst excretors can transmit infection for years if left untreated. Extraintestinal disease results when trophozoites breach the colonic mucosal barrier and enter the portal circulation. The organ affected most commonly is the liver, although cases of lung, brain, and skin involvement have been reported. The abscess usually is solitary, and the right lobe of the liver is affected most commonly (80%), a finding attributed to the right lobe receiving most of the

blood draining from the cecum and ascending colon.

Clinical Presentation

Most patients who have ALA present acutely (<10 days in duration) with fever, right upper quadrant abdominal pain, and weight loss. In general, amebic colitis precedes the development of ALA, but only 30% of patients report concurrent active dysentery. Hepatomegaly and weight loss often are encountered in patients who have a chronic illness (2 to 12 weeks in duration). Jaundice is unusual but may occur in patients who have severe disease and multiple abscesses. Cough may be present, and pulmonary examination may reveal dullness and rales in the right lung base. Approximately 4% to 9% of patients who have ALA may present with referred shoulder pain, which is related to involvement of the diaphragmatic surface of the liver. In neonates, ALA has a rapidly progressing course, mimicking neonatal sepsis.

Diagnosis

Laboratory abnormalities noted in patients afflicted with ALA include leukocytosis without eosinophilia, anemia, an elevated alkaline phosphatase, and minimal elevations in serum bilirubin and transaminase. Currently, serum antibody detection using indirect hemagglutination assay is the most useful diagnostic test for ALA and is positive in 95% to 99% of cases. It is unusual to find trophozoites in liver abscess aspirate. Stool microscopy usually is negative for *E histolytica* trophozoites or cysts. Molecular methods (using PCR) are the most sensitive for identifying and differentiating *Entamoeba* sp in stool. Chest radiography may reveal an elevated right hemidiaphragm and right-sided pleural effusion. Both ultrasonography and CT scan are sen-

sitive in the detection of ALA, but ultrasonography is the preferred method due to its low cost, availability, and lack of adverse effects.

Management and Outcome

Medical therapy with a 7- to 10-day course of intravenous or oral metronidazole alone can cure invasive disease in more than 95% of cases. Metronidazole is effective for elimination of both intestinal and extraintestinal infection. Percutaneous drainage is considered for large abscesses (>5 cm) to prevent spontaneous rupture, left-lobe abscesses that may rupture into the pericardial space, and failure to respond to medical therapy within 5 to 7 days. The need for open surgical drainage is rare. Following a course of metronidazole, patients should receive treatment with iodoquinol, paromomy-

cin, or diloxanide furoate to treat the luminal carrier state. Serial radiographic studies indicate that ALA usually resolves within 6 months of treatment. Antimotility agents and corticosteroids can worsen symptoms of amebiasis and, therefore, are not recommended.

Control measures for amebiasis include maintaining hand hygiene and good sanitation. Research is ongoing toward development of a vaccine against amebae. Oral and DNA-based vaccines have been tested successfully in animal models for immunogenicity and efficacy. Additional research is needed to determine the efficacy of the vaccine in humans.

Lessons for the Clinician

In developed nations where amebiasis is rare, failure to consider the in-

fection may delay diagnosis. Hepatic amebiasis may be encountered in immigrants from resource-limited countries even if they have no history of recent travel. ALA may be the first manifestation of amebiasis without any preceding diarrheal illness. The diagnosis should be considered if aspirated material does not show bacteria and serologic testing for *E histolytica* is positive. Treatment with metronidazole alone may be curative in 95% of those who have ALA. (James A. Owusu, Charles Turner, MD, Laurence B. Givner, MD, Avinash K. Shetty, MD, Wake Forest University Health Sciences and Brenner Children's Hospital, Winston-Salem, NC)

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

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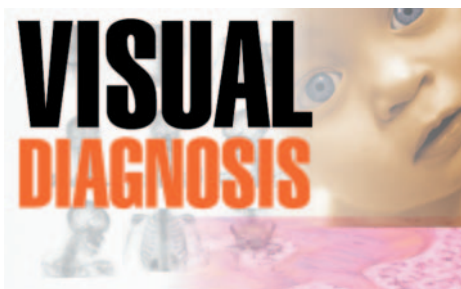
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The Intestinal Immune Barrier—Louis/Lin

Early Life Stress Induces Both Acute and Chronic Colonic Barrier Dysfunction—Gareau/Wine/Sherman

Index of Suspicion in the Nursery—Kakkilaya/Sangster/Kurepa/Hussein/Ibrahim

Strip of the Month: April 2009—Druzin/Peterson



Four Infants Who Have Red, “Bloody” Stools

Cases 1, 2, 3: Jill Lowers, MD,* Arthur Jaffe, MD,* Joseph A. Zenel, MD[†]; Case 4: Michael D. Cabana, MD, MPH,[§] Clement Donahue, MD,[†] Alan Uba, MD[†]



Figure 1. Red stool, guaiac-positive.



Figure 2. Red stool, guaiac-negative.

Case 1 Presentation

A 2-year-old, previously healthy boy presents to the clinic with a history of 24 hours of fussiness, decreased appetite, and several short-lived episodes of acute abdominal pain. During the past 8 hours he has had several red, “bloody” stools. There is no vomiting.

Physical examination reveals an alert child whose vital signs are normal. His abdomen is soft and nondistended. A palpable “mass” extends through the right upper and lower quadrants. Rectal examination does not reveal any fissures or tears. Auscultation reveals diminished bowel sounds. His remaining physical findings are within normal limits. After examination, the patient passes a red-colored stool (Fig. 1). Laboratory examination shows normal complete blood count and serum electrolyte concentrations. Stool guaiac testing is positive. Additional testing reveals the diagnosis.

Case 2 Presentation

A 2-year-old healthy girl presents with the complaint of a single large, red, “bloody” stool. She has had no vomiting, diarrhea, abdominal pain, fussiness, fever, or other systemic complaints. She has no history of constipation. Her mother brings the stool for examination (Fig. 2).

Physical examination reveals an alert, playful child whose vital signs are normal. Findings on abdominal examination are unremarkable, and the rectal examination does not reveal any fissures or tears. The remainder of her physical examination is normal. Stool guaiac testing is negative. Additional history reveals the diagnosis.

Case 3 Presentation

A 5-month-old boy who has a recent history of acute otitis media presents with three episodes of red, “bloody” stools in the past 48 hours. The child is otherwise well and has no vomiting, diarrhea, fever, or abdominal pain. His appetite is good, and he drinks 8 oz of formula every 3 to 4 hours. He has no prior history of constipation or formula intolerance. Currently, he is taking oral cefdinir for the otitis media. His mother brings a stool sample for examination (Fig. 3).

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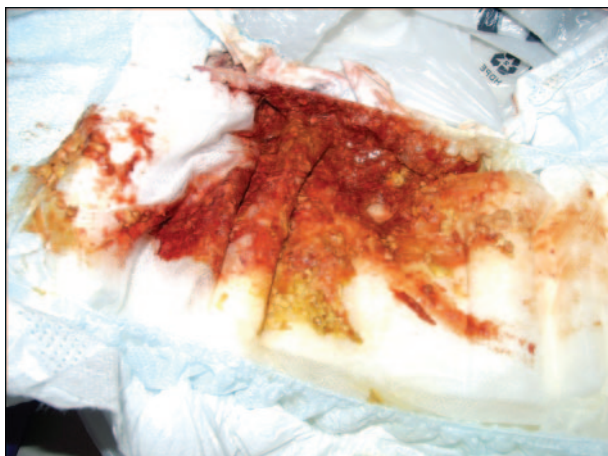


Figure 3. Red stool, guaiac-negative.

Physical examination reveals an alert and interactive infant whose vital signs are normal. His abdomen is benign, and the rectal examination reveals no fissures or tears. Other physical findings are unremarkable. Laboratory examination reveals a negative stool guaiac test. Additional investigation reveals the diagnosis.

Case 4 Presentation

A 6-month-old healthy boy presents to the clinic with the complaint of acute onset of “blood” in the diaper. Two hours ago, he had a large, red “bloody” stool. Earlier in

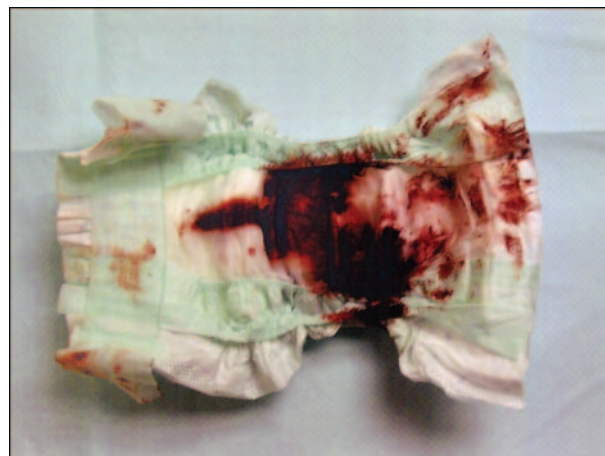


Figure 4. Red stool, guaiac-negative.

the day, he had two loose stools, but had no fever, vomiting, or diarrhea. He has been consuming 8 oz of formula every 3 to 4 hours and has no other systemic complaints. His mother brings a stool sample for examination (Fig. 4).

Physical examination reveals a comfortable child whose vital signs are normal. His abdomen is mildly distended but is soft and nontender and has no hepatosplenomegaly or masses. Other physical findings are unremarkable. Stool guaiac testing is negative. Additional history reveals the diagnosis.

Diagnoses

Case 1: Intussusception

The patient underwent an air contrast enema for suspected intussusception (Fig. 5). The diagnosis was confirmed and the intussusception reduced successfully without complication. The patient's bloody stools resolved, the intussusception did not recur, and the patient's appetite returned several days later.

Case 2: Cake Frosting Ingestion

Additional questioning of the mother revealed that the patient had eaten the entire contents of a 16-ounce can of red cake frosting the day before. She was not given any additional frosting, and there were no more red stools.

Case 3: Cefdinir-Iron Interaction

According to the cefdinir packet insert, there is a documented association of passing red-orange-colored stools by patients receiving oral cefdinir while on an iron diet. The reddish color is believed to be due to the formation of a nonabsorbable complex in the gastrointestinal tract between cefdinir or its breakdown products and iron (commonly found in infant formula). Although this drug-diet interaction is not harmful, families frequently request changing to another oral antibiotic medication because the stool color is distressing. This patient was switched to amoxicillin therapy to complete his antibiotic

course, and the red-colored stools resolved (as did the acute otitis media).

Case 4: Kool-Aid® Ingestion

After additional questioning, another adult caregiver revealed having modified the infant's diet that day. Earlier, he had consumed approximately 8 oz of strawberry-colored Kool-Aid®. The increased sugar load from the drink may have caused an osmotic diuresis, expediting stool transit time and allowing the artificial coloring to remain unchanged by digestion. The Kool-Aid® was discontinued, and there were no more episodes of red stools.

Discussion

Bloody stools are a relatively common chief complaint in pediatric primary care. Hematochezia, the passage of bloody bright red- or maroon-colored stools, is due to a distal gastrointestinal hemorrhage or to massive hemorrhage at a more proximal site above the colon. Although some ingested medications can cause gastrointestinal bleeding, many ingested foods or medications cause red stools that are commonly mistaken for "bloody." Therefore, it is important for the primary care clinician to be able to distinguish true bloody stools from other red-colored stools and to be acquainted with the broad differential diagnosis for hematochezia.

Obtaining an accurate history is essential for finding the cause of hematochezia. Key pieces of information include onset, frequency, and amount of the red stools; recent ingestions, travel, or ill contacts; and other associated symptoms. Physical examination may reveal the diagnosis or evidence of an ill child, but the findings generally are unrevealing. Therefore, it is essential to evaluate a stool sample for the presence of blood by performing a stool guaiac test. The results of the history and physical examination combined with the confirmed presence or absence of blood in the stool should help determine the appropriate underlying diagnosis.

Stool obtained from either a diaper or rectal examination is easily tested for the presence of blood by in-office observation of the conversion of guaiac from a colorless appearance to a blue color when combined with the stool sample. Guaiac is a leukodye, a substance that employs peroxidaselike activity found in hemoglobin to generate an oxidative reaction with a reagent to produce a blue color. The most common guaiac-containing fecal occult blood tests are Hemocult™ (Beckman Coulter Primary Care Diagnostics, Fullerton, Calif.), Seracult™ (Propper Manufacturing Co, Inc, Long Island City, NY), Colo-screen™ (Fisher Scientific, Philadelphia, Pa.), and HemoFEC™ (Roche Diagnostics, Indianapolis, Ind.).

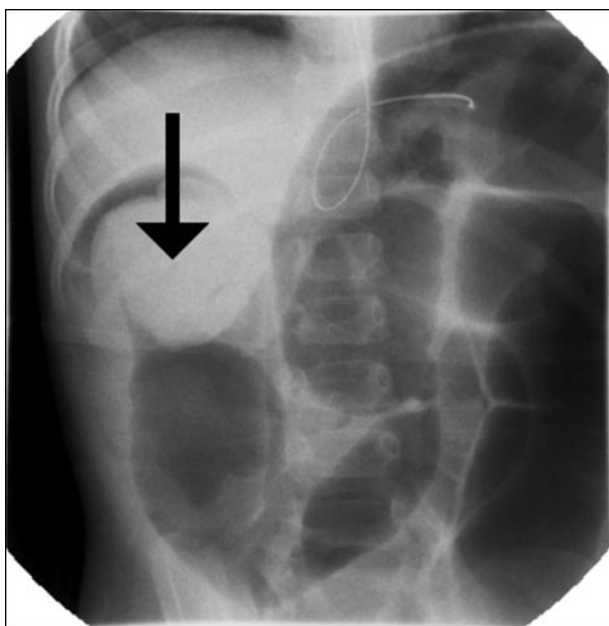


Figure 5. Air contrast enema with arrow pointing to intussusception.

Because the guaiac test relies on peroxidase activity, any substance that has peroxidase activity can cause a false-positive result, including rare red meat, horseradish, turnips, tomatoes, and fresh red cherries. In addition, low concentrations of ascorbic acid can inhibit hemoglobin peroxidase activity. As a result, vitamin C ingestion can lead to a false-negative result.

Common mimickers of hematochezia also include ingestion of red dye-containing foods such as red juices and other colored drinks, candy, and colored gelatin as well as tomatoes, beets, cranberries, and red peppers. Medications, including rifampin, diazepam syrup, ampicillin, and phenolphthalein (found in some laxatives), also can cause red stools that are mistaken for bloody stools. The stools appear red because of the natural or artificial coloring. However, stools containing these substances are guaiac-negative.

In the pediatric population, most causes of hematochezia are benign, but pediatric emergencies do occur. Differential diagnoses cover several major categories, including allergies, infections, intussusception, Meckel diverticulum, rectal fissures and tears, ingestions, and coagulation disorders.

Intussusception presents with the sudden onset of intense crampy abdominal pain, an abdominal mass, and late findings of currant jelly stools. Meckel diverticulum, a residual omphalomesenteric duct containing gastric mucosa that ulcerates adjacent tissue, generally presents with painless rectal bleeding. Colonic polyps are small outgrowths along the bowel wall that also present with painless rectal bleeding. Volvulus or midgut malrotation usually presents in infants who have bilious emesis, abdominal distention, and hematochezia. However, malrotation can present with chronic abdominal pain, distention, recurrent vomiting, or acute intestinal obstruction in older children. Anal fissures or tears often are associated with constipation. Children present with small amounts of bright red blood that streaks the surface of their stools.

Infants who have protein-induced proctocolitis or enterocolitis, whether breast- or bottle-fed, usually present with vomiting, fussiness, and poor weight gain and have blood-streaked or grossly bloody stools. Within weeks of dietary modification, symptoms improve. Inflammatory bowel disease, both ulcerative colitis and Crohn disease, may present with hematochezia, failure to thrive, weight loss, early satiety, abdominal pain, chronic

diarrhea, and fevers. Inflammatory bowel disease usually is diagnosed in the adolescent years, but may occur in younger children.

Infectious causes of bloody stools include infections with *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter jejuni*, *Clostridium difficile*, schistosomes, and viruses, including norovirus and rotavirus. Patients usually have self-limited bloody diarrhea, vomiting, and anorexia. *E coli* O157H is associated with hemolytic-uremic syndrome, which has a prodrome of bloody diarrhea, followed by anemia, thrombocytopenia, and renal failure.

Coagulation disorders, including thrombocytopenias and coagulopathies, may cause hematochezia. Of note, oral medications that may cause gastrointestinal irritation with bleeding include aspirin, indomethacin, ibuprofen, and corticosteroids.

Patient Courses

Of the four cases presented, only the child in Case 1 had hematochezia, indicating an emergent condition that was referred appropriately to a local emergency department for immediate treatment. The remaining three cases were mimickers of hematochezia that were diagnosed easily and treated in the outpatient setting.

Summary

The “bloody” stool is a common complaint in the primary care setting. Obtaining a history, performing a physical examination, and testing for fecal occult blood should help the practitioner distinguish hematochezia from the red stool due to ingestion of natural and artificial dyes and other substances that produce a red color. Although often benign, hematochezia may indicate significant underlying gastrointestinal pathology.

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Author Disclosure

Drs Golzari 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.

In 2003, Mana Golzari was a medical student at Stanford working at a juvenile detention medical center. She was struck by the poor health status of the incarcerated youth. Nationally, more than 2 million children and adolescents pass through juvenile detention each year, and they have substantially higher morbidity than their nonincarcerated peers. (1) Despite a 2001 American Academy of Pediatrics policy statement recommending establishment of a medical home before release and although it is mandated that incarcerated youth receive medical care, such services often are discontinued on the youth's discharge back into the community. (2)(3) Dr Golzari realized that the released youths were not being enrolled into public medical insurance programs for which they were eligible.

To address this barrier, Dr Golzari met in August 2005 with the legislative staff of representative Joe Coto, her state assembly member. She provided background research to support legislation ensuring Medicaid enrollment for eligible youth prior to release from detention. She worked with the staff to author a bill. It languished in committee, but they did

Rattling the Bars for Change: Medical Homes for Youth Exiting Juvenile Detention

not give up, instead developing support from the unions of parole officers and social workers, and teamed with California Senator Gil Cedillo's office to introduce Senate Bill (SB) 1469.

Dr Golzari worked continuously to broaden the coalition supporting SB 1469 with endorsements from psychologists, legal advocates, medical associations, and other stakeholders. She testified at legislative hearings about her first-hand experiences. She led letter-writing campaigns on behalf of pediatricians and sent Governor Schwarzenegger supporting materials, including a cost-benefit analysis.

As a resident since 2006 in the University of California at San Francisco Pediatric Leadership for the Underserved (PLUS) program, she has remained active on this issue. SB 1469 was passed into law in October 2006 and went into effect January 2008. In discussing her successful effort, Dr Golzari said, "I hope that conveying some of the nitty-gritty details about the legislative process will help other pediatricians meet with their local lawmakers to effect system change for overlooked pediatric patient populations like youth in detention."

Along with faculty collaborator Dr Anda Kuo, Dr Golzari has now established a partnership between San Francisco juvenile hall and her residency program and is working to establish a model system by which teens exiting detention have an initial appointment scheduled with a physician prior to release. They also have created a "Youth in Detention" cur-

riculum to disseminate best practices for this population and are conducting a study assessing medical care utilization patterns of recently released youth. (*Mana Golzari, MD, University of California, San Francisco, San Francisco, Calif.*)

SECTION EDITOR'S NOTE. Before he became governor and signed this bill into law, Arnold Schwarzenegger was perhaps best known for saying "I'll be back"—a catchphrase that may serve well as a motto for pediatrician advocates. Dr Golzari's efforts have been ongoing for 5 years and aren't over yet. Getting a law passed is just one step in effecting the desired change. In my "Pentad of Ps" for successful projects, one of the Ps stands for Planning, which also includes patience and persistence—attributes that this effort clearly embodies. (4) Sometimes advocacy happens easily, but oftentimes it requires rattling the bars for a long time. (*C. Andrew Aligne, MD, MPH*)

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Inborn Errors of Metabolism:

Part 2: Specific Disorders

Paul A. Levy, MD*

The following article is included online only as a second part of the article "Inborn Errors of Metabolism: Part 1."

Author Disclosure

Dr Levy did not disclose any financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Amino Acid Disorders

There is no one prototypical disorder of amino acid metabolism; each disorder has its own unique collection of symptoms. Four well-described amino acid disorders have been chosen as examples of this group.

Phenylketonuria, a disorder of phenylalanine metabolism, leads to intellectual disability if untreated.

Maple syrup urine disease involves an enzyme common to the degradation of the branched-chain amino acids (leucine, isoleucine, and valine). Although there are five subtypes of maple syrup urine disease, the classic form has a neonatal onset and generally progresses from poor feeding to coma and death if not treated.

Tyrosinemia also has multiple subtypes. Hepatorenal tyrosinemia (type I) may present with liver failure (elevated transaminase concentrations, hyperbilirubinemia, coagulopathy, ascites, and gastrointestinal bleeding) as well as kidney involvement (tubular dysfunction) and peripheral nerve involvement (painful crises, weakness or paralysis). Type II tyrosinemia is an oculocutaneous form of the disease that has corneal lesions and skin findings.

Homocystinuria, most commonly caused by cystathionine beta-synthase deficiency, presents with ocular (ectopia lentis), skeletal (marfanoid features such as dolichostenomelia and arachnodactyly), vascular (thromboembolic), and central nervous system (intellectual disability, stroke, and seizures) abnormalities.

When an amino acid disorder is suspected, measurement of plasma amino acids generally is sufficient to make the diagnosis. Assessment of urine amino acids can be helpful for homocystinuria and some abnormalities of amino acid transport (cystinuria, dicarboxylic amino aciduria) that affect the kidneys and for detecting generalized amino aciduria found with some kidney disease and mitochondrial disorders.

Urea Cycle Disorders

The degradation of amino acids results in their deamination, generating ammonia as the waste nitrogen. The urea cycle removes the excess ammonia by generating urea, which is eliminated in the urine. Six disorders of the urea cycle are known. Classic forms of urea cycle defects present in the first few days after birth with poor feeding, vomiting, tachypnea (sometimes with respiratory alkalosis), and lethargy that progresses to coma. There also are later-onset forms of many of the urea cycle disorders. Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder, so it occurs more commonly in males, although carrier females may become symptomatic sometime during their lifetimes. Only

Abbreviations

ALD:	adrenoleukodystrophy
AMN:	adrenomyeloneuropathy
CACT:	carnitine acylcarnitine translocase
CNS:	central nervous system
CPK:	creatine phosphokinase
CPS:	carbamyl phosphate synthetase
CPT:	carnitine palmitoyltransferase
CSF:	cerebrospinal fluid
GSD:	glycogen storage disease
LCAD:	long-chain acyl-coA dehydrogenase
LCFA:	long-chain fatty acid
MCAD:	medium-chain acyl-coA dehydrogenase
MLD:	metachromatic leukodystrophy
MPS:	mucopolysaccharidosis
mtDNA:	mitochondrial DNA
NAGS:	N-acetyl glutamate synthetase
nDNA:	nuclear DNA
OTC:	ornithine transcarbamylase
OXPHOS:	oxidative phosphorylation
RCDP:	rhizomelic chondroplasia punctuate
SCAD:	short-chain acyl-coA dehydrogenase
VLCAD:	very long-chain acyl-coA dehydrogenase
VLCFA:	very long-chain fatty acids

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arginase deficiency, a defect of the last step of the urea cycle, does not present with the hyperammonemia common to the other urea cycle disorders. Instead, it presents with neurologic manifestations (progressive spastic quadriplegia, tremor, choreoathetosis, ataxia, seizures, and slowing of cognitive development).

The difficulty with diagnosing the urea cycle disorders is their lack of biochemical abnormality on routine testing; electrolytes and liver enzyme values usually are normal. Many infants who have urea cycle defects initially are believed to have sepsis. Only if ammonia is measured in a sick neonate can the suggestion of a defect in the urea cycle be seen. Assessment of plasma amino acid concentrations often makes the diagnosis. Determination of the orotic acid value may be necessary to distinguish between OTC or carbamyl phosphate synthetase (CPS) deficiency and the rarer N-acetyl glutamate synthetase (NAGS) deficiency (OTC deficiency causes an elevated orotic acid concentration, whereas CPS and NAGS deficiencies are associated with normal or low orotic acid values).

Organic Acid Disorders

This group of disorders results from enzyme deficiencies in pathways of amino acid degradation. Defects in the metabolism of the branched-chain amino acids (leucine, isoleucine, valine) as well as tyrosine, homocysteine, methionine, threonine, lysine, hydroxylysine, and tryptophan are responsible for most of the 25 organic acid disorders. Some of these conditions have been described in only a few patients. The distinction between organic acid disorders and amino acid disorders, however artificial, generally stems from how the disorders are detected. Amino acid disorders are diagnosed by high-performance liquid chromatography amino acid analysis and organic acid disorders by urine organic acid analysis, usually by gas chromatography mass spectrometry.

Many disorders in this group present with acidosis, due to the nature of the accumulating metabolite. Hypoglycemia, lactic acidosis, and ketosis also may occur, either separately or in combination. Analysis of urine for organic acids is the mainstay of diagnosis, and an acylcarnitine profile often is helpful. This test can be performed on blood spotted on newborn screening filter paper.

Carbohydrate Disorders

Glycogen Storage Diseases (GSDs)

These disorders can be subdivided into those that present primarily with liver disease, those that can affect muscle and liver, and those that primarily affect muscle. Because the disorders were numbered in the order of their discovery, the numbers are not useful in separating the disorders

by clinical symptoms. GSD I, III, VI, and IX present with hepatomegaly and hypoglycemia. GSD III is subdivided into patients who have no muscle involvement (IIIb) and those who develop muscle weakness by their teenage years (IIIa). GSD IV leads to the formation of an abnormal glycogen that appears to be exceedingly noxious to the liver. Severe liver disease develops in the first few months after birth, leading to cirrhosis. Unlike the other primarily liver disorders, GSD IV often causes severe liver failure before the hypoglycemia is evident. GSD V, VII, and II primarily involve muscle. GSD II is unique in that it is a lysosomal storage disorder that presents in early childhood with progressive cardiomyopathy and hypotonia. GSD V and VII often present in adolescence with exercise intolerance and myoglobinuria.

Hypoglycemia and hepatomegaly suggest a GSD. Measuring concentrations of glucose, uric acid, lactic acid, liver transaminases, and lipids (cholesterol and triglycerides) generally is helpful. GSD I is distinguished from the other disorders that primarily affect liver by markedly elevated lactic acid as well as elevated uric acid and cholesterol concentrations. GSD III is characterized by normal or slightly increased concentrations of lactic acid, normal uric acid, but a greater elevation of triglycerides and cholesterol than GSD I. Creatinine phosphokinase (CPK) may be elevated in older children and adolescents if there is muscle involvement. GSD VI and IX have more benign courses than GSD I and III. Hypoglycemia is less severe, and hepatomegaly often resolves after puberty. Liver failure with portal hypertension suggests GSD IV. A liver biopsy usually is necessary to confirm the diagnosis of the liver GSDs, but DNA testing is increasingly available.

Myoglobinuria after exertion, with exercise intolerance that appears in adolescence, is highly suggestive of GSD V and VII. A muscle biopsy may be necessary to confirm the diagnosis. DNA testing now offers an alternative. DNA testing should help distinguish between type V and type VII.

Galactosemia

There are three disorders of galactose metabolism, but it is a deficiency of the second step of the pathway that is referred to as galactosemia. Infants who have classic galactosemia present with poor weight gain, poor feeding, vomiting, lethargy, jaundice, and hepatomegaly. They also are prone to sepsis from *Escherichia coli*. If the jaundice does not bring them to medical attention, it may resolve and the infants subsequently develop cirrho-

sis with portal hypertension and ascites. The diagnosis is confirmed by enzyme assay, usually on red blood cells

Hereditary Fructose Intolerance

The first exposure to fructose, usually from the disaccharide sucrose (fructose and glucose), results in vomiting and poor feeding. Continued exposure to fructose results in failure to thrive, hepatomegaly, hypoglycemia, jaundice, and renal dysfunction, followed by liver failure with clotting abnormalities, elevated liver transaminases, and ascites. Removal of fructose from the diet usually leads to rapid improvement, but this action requires suspicion of a problem with fructose. Elimination of other causes of hepatomegaly and hypoglycemia often suggest hereditary fructose intolerance. The diagnosis is confirmed by enzyme assay on a liver biopsy. DNA analysis is available for the common mutations.

Fructose-1,6-bisphosphatase Deficiency

Deficiency of this enzyme leads to hypoglycemia resulting from disruption of glucose production by gluconeogenesis. Hypoglycemia, lactic acidosis, and ketosis with hepatomegaly often are presenting signs. Generally, other disorders that cause both hypoglycemia and lactic acidosis need to be excluded. Improvement should be seen with removal of fructose from the diet. Confirmation is by enzyme assay on a liver biopsy.

Protein Glycosylation Disorders

This group of disorders is based on the relatively recent discovery of defects in protein glycosylation. As much as 50% of the body's proteins are modified with sugar (glycan) side chains. The glycan side chains modulate protein function, regulate protein half-life, provide structure (collagen and proteoglycans), and are involved in antibody recognition. Three types of linkage are used to modify proteins. N-linkage occurs with asparagine; O-linkage with serine, threonine, or hydroxylysine; and C-linkage with tryptophan. Defects with the formation of the N- and O-linkage have been reported, but not, as yet, for the C-linkage group.

N-linked glycosylation defects are referred to as congenital disorders of glycosylation. A characteristic of these disorders is the varied involvement of many organ systems. Intellectual disability, hypotonia, seizures, hepatic dysfunction, failure to thrive, vomiting, recurrent infections, and cerebellar hypoplasia are all features of this group.

O-linked glycoproteins are subdivided by the bridging sugar between the glycan side chain and the serine, threonine, or hydroxylysine amino acid in the protein.

Bridging sugars include N-acetylgalactosamine, galactosamine (O-galactosyl glycans), xylose (O-xylosyl glycans), mannose (O-mannosyl glycans), and fucose (O-fucosyl glycans).

Two disorders associated with xylose as the bridging sugar include a progeroid variant of Ehlers-Danlos syndrome and a multiple exostosis syndrome. Mannose sometimes is a bridge for glycoproteins found in brain, muscle, and nerves. Walker-Warburg syndrome, muscle-eye-brain disease, a limb girdle muscular dystrophy, and several other congenital muscular dystrophies have been reported to have defects of O-linked glycosylation.

The N-linked disorders can be diagnosed by transferrin electrophoresis. This glycosylated protein found in blood helps to identify the N-linked glycosylation defect. Diagnosis of the O-linked disorders is more difficult, and transferrin testing is not helpful. For this mannose-bridged group, immunostaining of muscle biopsy specimens can look for dystroglycan abnormalities. Electrophoresis of apolipoprotein C-III is useful for diagnosing mucin type proteoglycans (those with N-acetylgalactosamine as a bridge).

Lysosomal Disorders

Lysosomes are cellular organelles that contain more than 30 acid hydrolases that degrade complex cellular molecules to their building blocks. A deficient enzyme results in the accumulation or storage of an intermediate compound. Over time, this stored material leads to cellular damage and disease symptoms. Three groups of lysosomal storage disorders are discussed, and all involve complex organic molecules called glycoproteins. These molecules have a protein backbone to which a polysaccharide side chain (glycan) is attached.

The first group of disorders has deficiencies of lysosomal enzymes that degrade the polysaccharide chain (glycosaminoglycan) and lead to the mucopolysaccharidoses (MPSs). The second group has deficiencies of the enzymes that degrade glycoproteins with a less complex polysaccharide than the glycan involved in the MPSs. Molecules that have this simpler polysaccharide are termed oligosaccharides. The oligosaccharidoses include mannosidosis, sialidosis, fucosidosis, and aspartylglucosaminuria. The third group is the sphingolipidoses. This group involves glycoproteins with a backbone comprised of sphingosine and a long-chain fatty acid (LCFA) to produce ceramide. These sphingolipidoses include Fabry, Farber, Gaucher, Krabbe, and Niemann-Pick diseases, as well as G_{M1} and G_{M2} gangliosidoses and metachromatic leukodystrophy (MLD).

Mucopolysaccharidoses (MPSs)

Children who have an MPS disorder are normal at birth. The disorders are progressive, with most having neurologic involvement that leads to characteristic regression and loss of milestones. Most affected patients have intellectual disability. Hepatosplenomegaly is found in most of the disorders. Bone involvement leads to short stature and the characteristic radiologic findings (dysostosis multiplex). Many children who have MPS disorders have frequent bouts of otitis media.

The seven MPS disorders include three that have both central nervous system (CNS) and somatic involvement (MPS I: Hunter/Scheie syndrome, MPS II: Hunter syndrome, and MPS VII: Sly syndrome), one disorder that has somatic involvement but minimal CNS involvement (MPS VI: Maroteaux-Lamy syndrome), one disorder that has CNS involvement and minimal somatic involvement (MPS III: Sanfilippo syndrome), and two disorders that have bone or joint involvement (MPS IV: Morquio syndrome and MPS IX).

Coarsened facial features, hepatosplenomegaly, joint involvement, and developmental delay followed by regression are presenting features in children who have an MPS. Radiographs looking for evidence of bony involvement (dysostosis multiplex) often are helpful. A screening test may bolster the suspicion if the glycosaminoglycans are increased in the urine, but the diagnosis generally is confirmed by enzyme assay.

Oligosaccharidoses

This group is similar to the MPSs, with many disorders associated with coarsened facial features, hepatosplenomegaly, and retinal (cherry red spot) or corneal involvement. Regression also is found with this group of lysosomal storage disorders.

Urine tested for glycosaminoglycans is negative, despite the concern for an MPS disorder. Urine for oligosaccharides may suggest one of the disorders in this group. Radiographs show dysostosis multiplex for many of the oligosaccharidoses. In addition, alpha mannosidosis should be considered in the presence of severe dysostosis multiplex, hepatosplenomegaly, and intellectual disability. Beta-mannosidosis may be distinguished by hearing loss, sialidosis by cherry red spots and myoclonus, and fucosidosis by recurrent respiratory infections and angiokeratoma (similar to Fabry disease). An enzyme assay is used to confirm the suspected diagnosis in most cases.

Sphingolipidoses

The prominent features of this group include hepatosplenomegaly (Niemann-Pick disease, G_{M1} gangliosidosis, Gaucher disease), demyelination (Krabbe disease, MLD, G_{M1} and G_{M2} gangliosidoses), and neuronal storage (G_{M1} and G_{M2} gangliosidoses). Most of these disorders are characterized by neurologic regression.

Initial normal development followed by neurologic regression suggests a lysosomal storage disorder. Although a negative test for glycosaminoglycans and oligosaccharides in urine does not completely rule out an MPS or oligosaccharidosis, this finding does suggest consideration of a sphingolipidosis (which does not have any abnormality of glycosaminoglycans or oligosaccharides). Magnetic resonance imaging may show demyelination, and an ophthalmologic examination may reveal a cherry red spot. Diagnosis and confirmation generally are by enzyme assay.

Peroxisomal Disorders

Peroxisomes are cellular organelles involved in beta-oxidation of very long-chain fatty acids (VLCFAs), the degradation of phytanic acid by alpha-oxidation, and the synthesis of plasmalogens. Peroxisomal disorders can be divided into two groups: peroxisomal biogenesis disorders, typified by Zellweger syndrome, and disorders involving mutations of individual peroxisomal enzymes.

Zellweger Syndrome Spectrum Group

Peroxisomal biogenesis disorders fall into a spectrum, with Zellweger syndrome being the most severe, infantile Refsum disease being less severe, and neonatal adrenoleukodystrophy (ALD) being somewhat milder. Zellweger syndrome is the prototypical biogenesis disorder. It is characterized by dysmorphic features (high forehead, flat occiput, large anterior fontanelle, hypoplastic superior orbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils, and micrognathia), brain defects (migrational brain defects with microgyria, pachygyria, and dysmyelination) and seizures, liver disease (dysfunction and cirrhosis), adrenal insufficiency, and often, renal abnormalities (microcysts). Children suffer severe intellectual disability (little, if any, development) and die from multiple problems, often in the first postnatal year.

Due to the biogenesis defect, all of the peroxisomal enzymes are deficient. Patients generally accumulate VLCFAs and develop abnormalities in phytanic acid (high) and plasmalogens (low).

Rhizomelic Chondrodysplasia Punctata (RCDP)

The peroxisomal biogenesis disorders are due to defects in the importation of proteins produced in the cytosol into the peroxisomes. Another peroxisomal biogenesis disorder, RCDP, is due to an importation defect of a subset of peroxisomal enzymes that use a different recognition marker. Most of the peroxisomal enzymes normally are imported, with only a few that use the different recognition marker failing to reach their place within the peroxisome. B-oxidation of LCFAs and VLCFAs is unaffected, but phytanic acid alpha oxidation and plasmalogen synthesis are affected. Clinical features of the three types of RCDP are similar, but type 1 is a peroxisomal biogenesis defect, while types 2 and 3 are single-enzyme defects of peroxisomal enzymes. Patients have rhizomelic shortening of the limbs (humerus more than femur), joint contractures, congenital cataracts, calcific stippling of epiphyses of long bones, growth failure, and profound developmental delay.

VLCFA concentrations are normal. Red blood cell plasmalogens are low, and phytanic acid concentrations are elevated. For types 2 and 3 RCDP, only the red blood cell plasmalogens are low; phytanic acid values are normal. Care should be taken not to draw conclusions about normal phytanic acid values because, with the diet as the only source of phytanic acid, concentrations in young patients may be normal, only becoming elevated over time. Enzyme assays on fibroblasts or DNA analysis may be necessary to distinguish the different types of RCDP.

Peroxisomal B-oxidation of LCFAs and VLCFAs

A few deficiencies of the enzymes involved in the B-oxidation of VLCFA have been described. They generally present similarly to the Zellweger spectrum disorders. One disorder even has been reported to have a neuronal migration defect similar to the Zellweger spectrum disorders, which suggests that this abnormality in the Zellweger spectrum may be due to abnormal B-oxidation of LCFA and VLCFA.

Another disorder of peroxisomal B-oxidation, racemase deficiency, presents with a late-onset neuropathy, rather than a picture similar to the Zellweger spectrum disorders.

X-linked ALD

This disorder is presumed to involve a peroxisomal membrane protein that transports VLCFA into the peroxisomes. Although not an enzyme defect of the VLCFA pathway, failure of such transport leads to accumulation of VLCFA (C22:0, C24:0). Two phenotypes have been described. The first is a childhood cerebral form that has

an onset in the first decade after birth (mean age of 7 years) and has subtle initial manifestations of school behavioral problems (hyperactivity), emotional lability, and school failure. These initial features are followed by adrenal insufficiency and rapid progression of neurologic abnormalities believed to be due to an inflammatory reaction, with demyelination and gliosis of the parietal-occipital areas.

Adrenomyeloneuropathy (AMN) is a milder form of disease that presents with a later-onset, slowly progressive paraparesis (20s and 30s) that often is associated with adrenal insufficiency. AMN generally does not initially involve the brain, as does the childhood cerebral form of ALD, but 20% of affected patients eventually have brain abnormalities similar to those of childhood cerebral X-linked ALD. This group is referred to as AMN-cerebral.

Testing for elevation of VLCFA identifies patients who have defects of peroxisomal B-oxidation. Test results for other peroxisomal functions are normal. An enzyme assay on fibroblasts and DNA mutation analysis helps to separate the single-enzyme defects.

Plasmalogen Synthesis

Two enzyme defects of plasmalogen synthesis have been identified and present with a clinical picture similar to that of RCDP. In fact, the two defects are referred to as RCDP types 2 and 3. As with RCDP type 1, plasmalogen values are low, and this compound can be measured in red blood cells. Studies on skin fibroblasts often are necessary to distinguish the type of RCDP.

Peroxisomal Alpha-oxidation of Fatty Acids

Phytanic acid, a branched-chain fatty acid, whose only source is from dietary intake, undergoes alpha-oxidation in peroxisomes. Loss of this pathway results in accumulation of phytanic acid, which is the cause of Refsum disease (not infantile Refsum disease, which is a peroxisomal biogenesis disorder in the Zellweger spectrum). Clinically, Refsum disease is characterized by a tetrad of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and increased cerebrospinal fluid (CSF) protein without increased cells. Symptoms usually are apparent before 20 years of age, with night blindness often being the first clinical symptom. Loss of the sense of smell and hearing loss also are common.

For patients who have Refsum disease, only phytanic acid concentrations are elevated. Although patients who have the Zellweger spectrum of disorders have elevated phytanic acid concentrations, VLCFA values also are abnormal.

Mitochondrial Fatty Acid Oxidation Defects and Carnitine Transport Defects

Mitochondrial Fatty Acid Oxidation Defects

Four enzymatic reactions are involved in the removal of 2-carbon fragments as acetyl-CoA from saturated fatty acids, which then are used for energy production. These steps are repeated in a spiral of β -oxidation that continues until only one 2-carbon fragment is left. Each of the four steps involved in β -oxidation of fatty acids has two or more enzymes that show specificity for different length fatty acids. The first step (acyl-CoA dehydrogenase) has four different enzymes, each with its own specificity. Short-chain acyl-CoA dehydrogenase (SCAD) shows specificity for fatty acids that are 4 to 6 carbons in length, medium-chain acyl-CoA dehydrogenase (MCAD) for those of 4 to 12 carbons, long-chain acyl-CoA dehydrogenase (LCAD) for those of 12 to 18 carbons, and very long-chain acyl-CoA dehydrogenase (VLCAD) for fatty acids 14 to 20 carbons in length. Disorders involving deficiencies of SCAD, MCAD, and VLCAD have been described, but patients who have deficiencies of LCAD have yet to be identified.

The third step has two known disorders and involves one of two 3-hydroxyacyl-CoA dehydrogenases. The first, short-chain 3-hydroxyacyl-CoA dehydrogenase, despite its name, acts on fatty acids of 4 to 16 carbons in length. The second, long-chain 3-hydroxyacyl-CoA dehydrogenase, favors the longer-chain fatty acids.

The unifying feature for disorders of mitochondrial fatty acid oxidation is the presence of hypoketotic hypoglycemia. SCAD, which catalyzes the last step and has C4 (butyl-CoA) as a substrate, may be the exception and rarely presents with hypoglycemia. Some of the enzyme deficiencies have a variant form, which produces myoglobinuria and muscle weakness. In general, if a fatty acid oxidation disorder is being considered, glucose concentration (both in the laboratory and by finger stick) should be measured, as well as concentrations of electrolytes, ammonia, liver transaminases, CPK, lactic acid, and uric acid. A complete blood count also should be obtained. Urine should be assessed for organic acids, and a routine urinalysis should be performed to help determine if there is myoglobinuria (positive blood on urinalysis but no red blood cells on microanalysis). An acylcarnitine profile can be helpful, as can assessment of urine for organic acids. A skin biopsy may be needed for enzyme analysis on fibroblasts to narrow down the actual enzymatic defect.

Carnitine Transport Defects

Carnitine helps to transport the longer-chain fatty acids (14 to 20 carbons in length) into mitochondria because unlike the medium-chain and short-chain fatty acids, they cannot pass through the mitochondrial membrane without assistance. Carnitine palmitoyltransferase I (CPT I) attaches carnitine to the fatty acid molecule, carnitine acylcarnitine translocase (CACT) transports the resulting molecule across the mitochondrial membrane, and finally, CPT II removes the carnitine and releases the fatty acid for β -oxidation.

Defects in the carnitine transport enzymes share some of the features of fatty acid oxidation defects, such as manifesting with hypoglycemia associated with hypoketosis, lethargy, and sometimes a Reye-like syndrome (hepatomegaly, elevated transaminases and ammonia). Seizures are not uncommon because of the hypoglycemia. The most common presentation of CPT II is an adult onset that involves muscle weakness, elevated CPK, and myoglobinuria after prolonged exertion.

If a carnitine transport defect is suspected, an acylcarnitine profile is a helpful initial test. CPT II and CACT have similar abnormalities that distinguish them from CPT I. In addition, CPT I may have normal-to-elevated carnitine concentrations. A skin biopsy with fibroblast studies may be necessary to distinguish between these disorders.

Mitochondrial Disease

Mitochondrial Disease Due to Mitochondrial DNA Alterations

As noted previously, mitochondria are involved in fatty acid oxidation (including carnitine transport). Mitochondria also have a role in the urea cycle, citric acid cycle, and most importantly, the energy production pathway of oxidative phosphorylation (OXPHOS). It is for defects in the energy-producing pathway, OXPHOS, that the term mitochondrial disease is reserved.

Mitochondria have their own DNA (mtDNA). The circular molecule encodes 37 proteins, including a translational system (2 ribosomal RNAs and 22 tRNAs) that differs from the cellular protein synthesis components and 13 OXPHOS proteins. The remaining (more than 70) OXPHOS proteins as well as nearly 900 proteins involved in other mitochondrial pathways are encoded by the nuclear DNA (nDNA). All mitochondria are derived from the ovum, so mtDNA disorders are maternally inherited. Mitochondrial disease due to nDNA mutations have been reported to have autosomal recessive, autosomal dominant, and X-linked inheritance patterns.

Mitochondria have multiple copies (3 to 10) of the mtDNA. Not all of the hundreds of mitochondria in the ovum are incorporated into the developing embryo. If incorporated into the embryo, the abnormal mitochondria may not be distributed equally to all tissues. The presence of different mtDNA molecules within a cell or individual is referred to as heteroplasmy. Energy production is affected by the presence of heteroplasmy within a mitochondrion. The mitochondria harboring mtDNA mutations generally are less able to produce energy. Clinical symptoms become apparent when the energy production is below the energy requirements of a particular tissue. Tissues that have high energy requirements, such as brain, liver, and kidney, are more susceptible to mitochondrial disease.

A number of mtDNA disorders have been described. Kearns-Sayre syndrome, Pearson syndrome, and chronic progressive external ophthalmoplegia (CPEO) have deletions or duplications of the mtDNA. MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), MERRF (myoclonic epilepsy with ragged red fibers), NARP (neurogenic weakness, ataxia, and retinitis pigmentosa), MILS (maternally inherited Leigh syndrome), hypertrophic cardiomyopathy, mitochondrial myopathy, LHON (Leber hereditary optic neuropathy), and SNHL (nonsyndromic aminoglycoside-induced sensory neural hearing loss) have point mutations of the mtDNA.

Mitochondrial Disease (OXPHOS) Due to Nuclear DNA Mutations

Because most of the mitochondrial genes are coded by nDNA, it is not surprising that now more than 30 known OXPHOS disorders are due to nDNA mutations. Some of these disorders involve OXPHOS genes directly, some

involve the importation of mitochondrial enzymes synthesized in the cytosol, and others affect mtDNA synthesis or importation of nucleotides or nucleotide synthesis.

Diagnostic Testing

Mitochondrial disease can affect many types of tissues. Brain, heart, liver, kidney, and pancreas involvement, as well as hearing loss and endocrine dysfunction have been reported. Often, muscle weakness, stroke, cardiomyopathy, hearing loss, or endocrine dysfunction suggests a mitochondrial disorder. In fact, the somewhat unrelated involvement of multiple tissues often adds mitochondrial disease to the differential diagnosis.

Screening with lactic acid cannot identify all patients who have mitochondrial disease because this is an inconsistent finding with the disorders. A markedly elevated lactate concentration, however, should raise concern about a mitochondrial disorder. Elevation of lactate often occurs after use of a tourniquet, but the elevation also can be caused by dehydration, seizure activity, or improper specimen handling.

Determination of a lactate-to-pyruvate ratio may be helpful; a ratio greater than 30 is indicative of an OXPHOS defect. CSF lactate and pyruvate values also are helpful for some patients.

A biopsy, generally of muscle, is the most definitive method for diagnosis. The specimen should be examined for ragged red fibers as well as accumulation of mitochondria in the subsarcolemma layer of the muscle. Staining for succinate dehydrogenase and cytochrome C oxidase should be performed. Electron microscopy may show abnormal mitochondria or crystalline inclusions. A muscle specimen should be sent to a specialized laboratory for enzyme analysis of the OXPHOS pathway.

Complementary, Holistic, and Integrative Medicine: Fish Oils and Neurodevelopmental Disorders

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Introduction

Omega-3 and omega-6 fatty acids are essential to human health and development. During the last century, intake of omega-6-rich foods (eg, plant-based oils) increased, while that of omega-3-rich foods (eg, fish and fish oils) decreased. (1)(2) The recommended ratio for dietary intake of omega-6:omega-3 ranges from 4:1 to 7.5:1. (3) The modern western diet is deficient in omega-3 fatty acids; (4) recent data suggest a 17:1 to 25:1 ratio in North America. (5)(6)(7) Evidence suggests that omega-3 deficiencies may play a role in neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), dyslexia, dyspraxia, developmental coordination disorder (DCD), and the autism spectrum disorders (ASDs). These conditions are increasingly prevalent in western societies, with estimated prevalence rates of more than 10% in children. (8) Such conditions share a number of features: 1) affected children often experience problems in motor or oculomotor function, language development and proficiency, social skills, and visual and auditory processing; 2) the disorders are disproportionately more prevalent among males; 3) there is substantial comorbidity among the disorders; and 4) the disorders often cluster in families. (7)(8)(9)(10) This review describes the effects of omega-3 fatty acid on the course and outcome of neurodevelopmental disorders.

Pharmacologic Action

The most important omega-3 fatty acids for cognitive development are the polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). (7) These essential fatty acids (EFAs) are synthesized in the body from alpha-linolenic acid, but because the conversion process is inefficient, (11)(12) EPA and DHA must be provided by the diet. Known to have anti-inflammatory effects, the omega-3 fatty acids inhibit platelet aggregation (13) and are critical for brain development and function. (7)

Evidence of Efficacy

ADHD

The role of PUFAs in ADHD, a disorder characterized by inattention, hyperactivity, and impulsivity, was hypothesized initially by Colquhoun and Bunday in 1981. (14) The authors administered a survey to children belonging to the Hyperactive Children's Support Group and concluded that many participants were deficient in PUFAs.

Blood biochemical studies have provided support for the hypothesis that children afflicted with ADHD are deficient in PUFAs or have problems with fatty acid metabolism. (15)(16)(17)(18)(19) In addition, animal studies have shown that omega-3 deficiency throughout gestation and lactation is related to attention and behavioral dysfunctions comparable with those seen in ADHD. (20)

Studies examining the clinical effects of PUFAs on ADHD symptoms have produced mixed results. Two randomized, controlled trials (RCTs) of DHA alone compared with EPA alone or a combination showed no significant treatment effect. (21)(22) For example, Voigt and associates (22) administered 345 mg per day of DHA for 4 months to 32 children who had ADHD and found no statistically significant differences between these

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NOTE: The agents discussed in this series are designated as dietary supplements rather than drugs. Although dietary supplements are regulated by the United States Food and Drug Administration (FDA), their manufacturers may make claims with little evidence and need not prove safety prior to marketing. The burden is on the FDA to monitor safety after the product is on the market. Readers are referred to the 1994 Dietary Supplement Health and Education Act (www.cfsan.fda.gov/~dms/dietsupp.html).

children and a placebo group on measures of attention or impulsivity. However, studies in which the treatment group received a combination of DHA and EPA have reported greater treatment effects, suggesting that EPA or a combination is responsible for any benefits. (7)(23)(24)(25)(26) One RCT involved 41 children (ages 8 to 12 years) diagnosed as having DCD, who were suspected of having dyslexia and who displayed ADHD-like symptoms. (25) After receiving daily supplementation of either 186 mg EPA and 480 mg DHA or olive oil placebo, the treatment group received significantly lower scores on scales of inattention compared with the placebo group and improved in three of seven ADHD scales compared with baseline. Within the placebo group, there were no significant improvements on any scale compared with baseline.

A similar RCT, in which 50 children ages 6 to 13 years who had ADHD-like symptoms and behaviors received either 480 mg DHA and 80 mg EPA or olive oil placebo daily for 4 months, found that EPA+DHA supplementation was related to significant improvements in parental ratings of conduct and teacher ratings of attention compared with the placebo group. (26) However, the treatment group showed no improvement over the placebo group in 14 of the 16 outcome measures used. Two recent RCTs, one from Australia (27) and one from Italy, (28) reported some beneficial treatment effects. Sinn and Bryan (27) measured the effects of fatty acid supplementation (558 mg EPA, 174 mg DHA, 60 mg gamma-linolenic acid [GLA], and 1,038 mg vitamin E), fatty acid plus multivitamin/mineral supplementation, and placebo on learning and behavioral problems in 132 children. Eligible children were 7 to 12 years of age, had scored in the 90th percentile on the Connors abbreviated ADHD index, (29) and were not taking any stimulant

medication or recent omega-3 supplementation. After 15 weeks, the treatment groups showed significant improvement on 9 of 14 parent rating scales but not on any teacher rating scales. Although participants were matched with similar controls, the regional pilot study of Germano and associates (28) did not have a placebo group. However, it is the only study that has used dosing according to body weight (2.5 g/10 kg per day), with an EPA:DHA ratio of 1.89. After 8 weeks of consuming a mean daily dose of 0.234 g/10 kg fish oil, 16 children (ages 3.5 to 16 years) experienced significant reductions in inattention and hyperactivity. Clinical improvement (based on score differences) did not appear to be related linearly to fish oil dose. High rates of dropout and low compliance were limiting factors in both of these recent studies. Furthermore, a limitation of three studies (25)(26)(27) is that inclusion was based on ADHD symptoms rather than on formal ADHD diagnosis.

Available data are inconclusive as to the beneficial effects of PUFAs on ADHD-related behaviors. Some degree of positive treatment effect has been reported for most trials, but as other authors have noted, (7)(30)(31) drawing conclusions regarding the efficacy of PUFAs for treating ADHD symptoms is limited by inconsistent methodologies, including different inclusion criteria, doses and ratios of EPA and DHA, study lengths, and outcome measures.

Dyslexia

Dyslexia is a language-based learning disability characterized by specific difficulties in reading and spelling as well as written language. A 1985 case study found that an affected child had clinical signs of fatty acid deficiency, including dry hair and dandruff, weak fingernails, and rough and dry skin; subsequent blood testing confirmed a fatty acid deficiency. Supplementation alleviated the symptoms and improved the child's school performance. (32) Richardson and associates (33) found that higher fatty acid deficiency scores among males were related to poorer reading and spelling ability as well as to poorer performance on recall of digits, a measure of auditory working memory. Recently, an open study was conducted in Sweden with 19 children (ages 9 to 17 years) diagnosed as having dyslexia. (34) After 20 weeks of receiving daily doses of 108 mg EPA, 480 mg DHA, 96 mg GLA, 35 mg arachidonic acid (AA), and an unspecified amount of vitamin E, children experienced improvements in reading speed and general schoolwork, based on word-chain tests as well as on parent and child subjective evaluations.

No fish oil RCT has been conducted with children

Abbreviations

AA:	arachidonic acid
ADHD:	attention-deficit/hyperactivity disorder
ASD:	autism spectrum disorder
DCD:	developmental coordination disorder
DHA:	docosahexaenoic acid
EFA:	essential fatty acid
EPA:	eicosapentaenoic acid
GLA:	gamma-linolenic acid
PCB:	polychlorinated biphenyls
PUFA:	polyunsaturated fatty acid
RCT:	randomized, controlled trial

who are formally diagnosed as having dyslexia. An RCT by Richardson and Puri (25) that involved children suspected of having dyslexia had promising results, as described previously. The 22 children given PUFA supplementation had significantly improved scores on measures of inattention and general behavioral problems compared with the 19 children who received placebo, and the treated children showed significant reductions on several ADHD subscales compared with baseline. The placebo group did not have significant improvements on any scale but showed symptom reductions similar to the original treatment group after a 12-week crossover period, during which time they also received fish oil supplementation. This finding suggests that additional study is warranted to determine whether children meeting well-defined criteria for dyslexia may benefit from EFA supplementation.

Motor Coordination Disorders

Dyspraxia involves specific impairments of motor function and motor planning. Along with DCD, which involves marked impairments in motor coordination, dyspraxia commonly is associated with learning, organizational, and behavioral difficulties as well as psychosocial maladjustment. (35)(36) One small open study, in which 15 children who had dyspraxia were tested before and after 4 months of daily supplementation with a mixture that provided 480 mg DHA, 35 mg AA, and 96 mg GLA, found that supplementation was associated with significant improvements in motor skills. (37) The only RCT to date was a crossover trial of 117 children ages 5 to 12 years who had DCD and received either 3 months of daily supplementation with 558 mg EPA, 174 mg DHA, and 60 mg GLA or olive oil placebo. (23) Although the treatment group did not display significant improvements in motor skills compared with the placebo group, their spelling and reading scores improved significantly compared with those of the control group. They also displayed significant reductions in ADHD-related symptoms, as assessed by the Connors Teachers Rating Scale. After a 3-month crossover, wherein the placebo group received supplementation, this group showed improvements in reading, spelling, and ADHD symptoms similar to children in the original active treatment group.

ASDs

Patients diagnosed with ASD exhibit restricted patterns of behavior, behavior disturbances, language abnormalities, and marked impairment in social interaction. (38)(39) Blood biochemical studies have reached mixed conclusions as to whether children who have ASD have

abnormal PUFA concentrations. In two studies, children who had ASD, compared with children who did not have this diagnosis, had reduced EFA concentrations in plasma (40) and red blood cells. (9) However, in a third study, published most recently, 16 children ages 12 to 20 years old who had ASD had elevated concentrations of DHA in plasma compared with the control group. (41)

Supplementation studies in children who have ASD have been few. Bell and associates (9) found that supplementation with EPA-rich fish oils for at least 6 months in nine children diagnosed as having ASD (compared with 18 unsupplemented children who had ASD and 55 controls) resulted in improvements in general health, sleep patterns, cognitive and motor skills, concentration, eye contact, and sociability as well as reductions in infection, irritability, aggression, and hyperactivity, as reported by parents. However, this was an open-label study, which limits the validity of the results. The first double-blind, placebo-controlled RCT, a pilot study, was conducted in Austria in 2007. (38) Seven children ages 5 to 17 years received daily fish oil supplementation (840 mg EPA, 700 mg DHA, 7 mg vitamin E) while six matched controls received coconut oil placebo. After 6 weeks, no significant differences between the groups were found, although the treatment group had reductions in hyperactivity and stereotypy compared with the control group. The small sample size and relatively short study period limit the ability to draw firm conclusions.

Safety Profile

The safety profile of omega-3 fatty acids generally is favorable. Only two studies described previously reported treatment-related adverse events. Sinn and colleagues (42) reported two cases of slight nausea and one of nose bleeds, and Amminger and associates (38) reported a case of mild fever. Fish oil can cause an unpleasant fishy aftertaste or “fishy burp,” which may increase the risk of noncompliance. Other potential adverse effects include gastrointestinal upset (flatulence, pain, diarrhea, belching, heartburn, nausea), altered immune response, reduced blood pressure, and increased risk of bleeding (at high doses). (43)(44) Fish oil may interact with anticoagulants (eg, warfarin) or antiplatelet drugs (eg, aspirin) (45)(46)(47)(48) and oppose the action of statin drugs. Supplements should be used cautiously in patients at high risk for hemorrhagic stroke (49) as well as those in the postoperative period or taking any of the previously noted medications. (45)

Recommended Dose

The United States Food and Drug Administration considers a daily intake of less than 3 g EPA+DHA to be generally safe, including in the preoperative period; higher intake may increase the incidence of adverse effects. (50) Dose recommendations for children have not been firmly established. Fatty fish consumed in large amounts may be unsafe due to potentially significant amounts of toxins such as mercury, polychlorinated biphenyls (PCBs), dioxin, and dioxin-related compounds. However, fish oil in the form of supplements contains little-to-no mercury and low concentrations of PCBs and toxins. (51)(52) Parents should consult their child's pediatric clinician before starting any fish oil supplementation.

Conclusion

Neurodevelopmental disorders have complex etiologies involving both genetic and environmental factors. Objective biologic markers for many of the disorders have yet to be identified. (7) Fish oil supplementation, especially with supplements containing EPA, may lead to improvements in learning and behavior in some children who have neurodevelopmental disorders. However, the evidence is mixed and its interpretation limited by variability in study design and inclusion criteria. Future large, well-designed studies are needed to illuminate the relationship between omega-3 fatty acids and neurodevelopmental disorders.

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