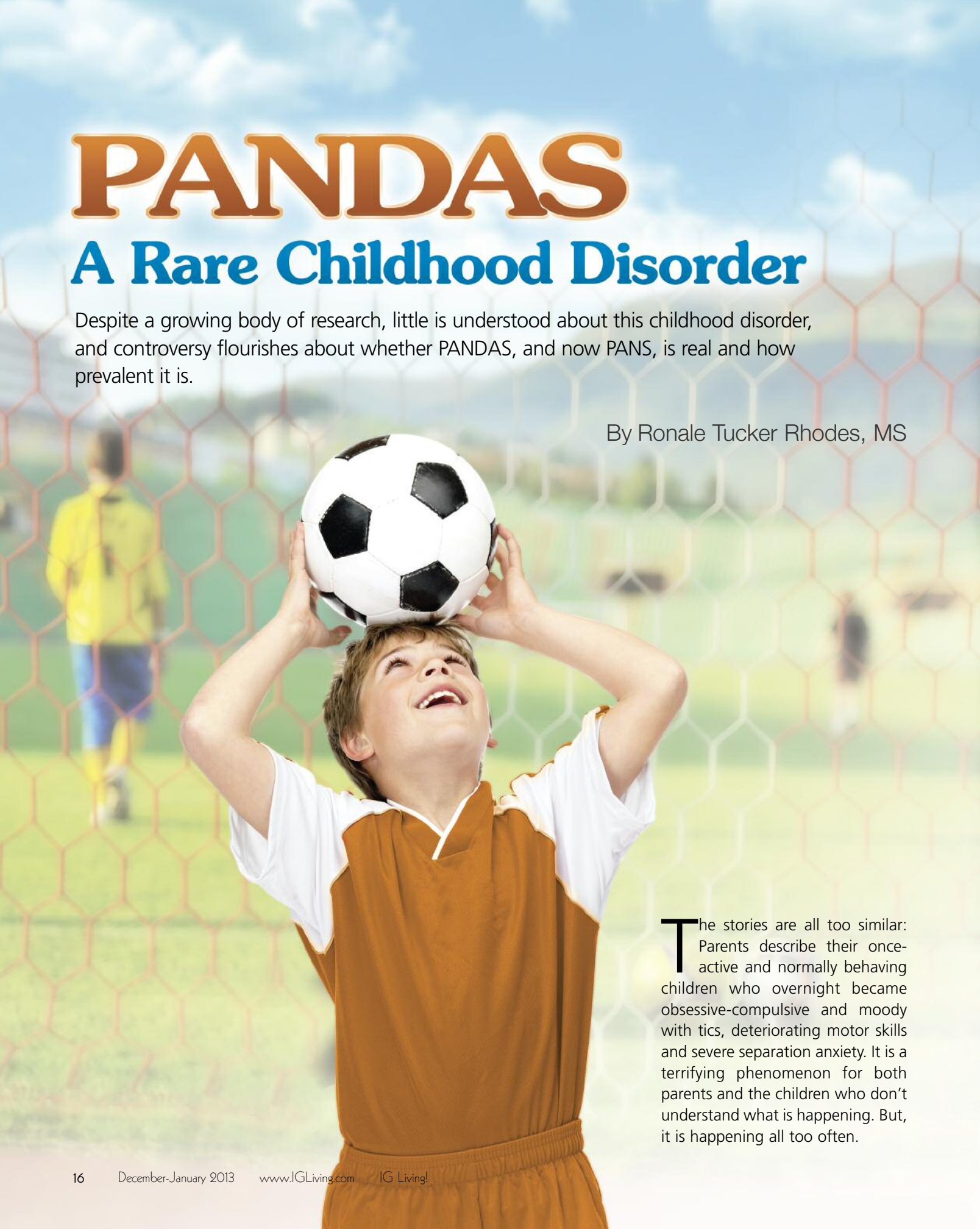
PANDAS

A Rare Childhood Disorder

Despite a growing body of research, little is understood about this childhood disorder, and controversy flourishes about whether PANDAS, and now PANS, is real and how prevalent it is.

By Ronale Tucker Rhodes, MS



The stories are all too similar: Parents describe their once-active and normally behaving children who overnight became obsessive-compulsive and moody with tics, deteriorating motor skills and severe separation anxiety. It is a terrifying phenomenon for both parents and the children who don't understand what is happening. But, it is happening all too often.

The problem is that the true prevalence of PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections), and now PANS (pediatric acute-onset neuropsychiatric syndrome), is not known. Even worse, despite the growing body of research behind the disease, there is still too much that is unknown, and some medical professionals refuse to believe it exists.

What Is PANDAS?

The term PANDAS is used to describe a subset of children and adolescents who have obsessive compulsive disorder (OCD) and/or tic disorders whose symptoms worsen following strep infections such as strep throat and scarlet fever.[1] It is listed as a rare disease by the Office of Rare Diseases of the National Institutes of Health, meaning PANDAS affects less than 200,000 people in the U.S.[2] According to the PANDAS Network, a conservative estimate of the number of PANDAS cases in the U.S. is 162,000. However, the true prevalence is unknown. It is known that the ratio of boys to girls over 8 years old who have PANDAS is 2.6 to 1, and under 8 years old, it is 4.7 to 1. Based on a survey of 700 family self-reports to PANDAS Network.org, the onset of PANDAS occurred between ages 1 to 3 in 11 percent of those families, ages 4 to 9 in 69 percent, ages 10 to 13 in 19 percent and ages 14 and older in 1 percent. The primary symptoms described by the families were OCD (37 percent), tics (14 percent) and both (49 percent). And, the infections reported by the families were strep (81 percent) or others, such as mycoplasma, lyme disease, etc. (19 percent).[3]

PANDAS was first observed in the 1980s when researchers at the National Institute of Mental Health (NIMH) were studying childhood-onset OCD. The researchers, who included Drs. Susan Swedo, Henrietta Leonard and Judith Rapoport, observed that some of the children had an unusually abrupt onset of symptoms unlike typical cases of OCD. Rather than symptoms beginning gradually and, in many instances, hidden by the child for weeks or months because of their embarrassment, the symptoms of the children in the PANDAS subgroup occurred very suddenly (overnight or out of the blue) and with dramatic onset (within 24 to 48 hours). In addition to the OCD and tic symptoms, these PANDAS children experienced a variety of other neuropsychiatric symptoms, including separation anxiety, anxiety attacks, irritability, extreme mood swings, temper tantrums, immature behaviors (like baby talking), hyperactivity, problems with attention and concentration, handwriting changes and problems with math, reading and other school subjects. The NIMH researchers discovered that all of the symptoms usually occurred following a strong stimulant to the immune system such as a viral infection or bacterial infection. These first cases were given the name PITANDS (pediatric infection triggered autoimmune neuropsychiatric disorders), but when it was discovered they followed infections with influenza, varicella (chicken pox) and streptococcal bacteria (strep throat and scarlet fever), the researchers later decided to focus on OCD symptoms that occurred after streptococcal infections because of the connection between OCD and Sydenham chorea, the neurological form of rheumatic fever. Hence, the disease was renamed PANDAS.[1]

Despite the growing body of research behind PANDAS, there is still too much that is unknown, and some medical professionals refuse to believe it exists.

Because it is often difficult to demonstrate the relationship between strep infections and OCD/tic symptoms, which can result in delayed diagnosis and treatment of affected children, clinicians and researchers met in 2010 at the National Institutes of Health to discuss changing the diagnostic criteria. As a result, the PANDAS criteria were modified to describe PANS, which encompasses the larger class of acute-onset OCD cases. PANS and PANDAS are comparable to cancer and leukemia (respectively), as PANS is the large class of disorders and PANDAS is one specific type.[1]

A Controversial Diagnosis

One of the reasons a PANDAS diagnosis is so controversial is because some physicians say there isn't enough evidence to prove that strep or a similar infection can lead to OCD. The PANDAS hypothesis was based on observations in

clinical case studies at the NIH and in subsequent clinical trials where children appeared to have dramatic and sudden OCD exacerbations and tic disorders following infections. Yet, while there is supportive evidence for the link between strep and onset in some cases of OCD and tics, proof of causality has remained elusive.[4]

At present, determining whether a child has PANDAS can be based only on a clinical diagnosis, meaning the diagnosis is made on the basis of knowledge obtained by medical history and physical examination alone, without benefit of laboratory tests. Clinicians use five diagnostic criteria for the diagnosis of PANDAS: 1) presence of OCD and/or a tic disorder, 2) pediatric onset of symptoms (ages 3 years to puberty), 3) episodic course of symptom severity, 4) association with group A beta-hemolytic streptococcal infection (a positive throat culture for strep or history of scarlet fever) and 5) association with neurological abnormalities (motoric hyperactivity or adventitious movements such as choreiform movements).[5]

Children with PANDAS also seem to have dramatic ups and downs in their OCD and/or tic severity. Whereas children with OCD may have good days and bad days or even good weeks and bad weeks, children with PANDAS have a very sudden onset or worsening of their symptoms,

Kap's Story

In January 2011, 10-year-old Kap Smith started coughing nonstop. It started not long after his sister contracted a strep infection and Kap complained of a sore throat. Assuming Kap also had strep, his pediatrician prescribed antibiotics, but they didn't heal his sore throat; instead, Kap also was lethargic and, then, out of the blue, his cough developed.

For three months, Kap's doctor tried to figure out what was wrong with him. He was treated for allergies; he was sent to a therapist for depression; he was hypnotized — but nothing worked. "He was exhausted," said Kap's mom, Kristi. "He looked wiped out, and he didn't sleep at night." As a last resort, Kap was sent to National Jewish Health in Denver, Colo., a 30-minute drive from his home in Boulder. National Jewish is considered the No. 1 respiratory hospital in the nation. A doctor there diagnosed Kap with PANDAS. "I was just blown away when she wrote it down as PANDAS," said Kristi. "I felt like we were starting all over again."

Kap was sent to Children's Hospital for treatment. But, they didn't believe the diagnosis. "They said the jury is still out on PANDAS," explained Kristi. "And they put him on meds that made him crazy. He would hide in closets. He was out of school for about four months. At that point, I told a friend about it, and she knew another gal whose kid had PANDAS, and he couldn't leave his home or mom." That friend's child was treated for PANDAS by a physician in Chicago.

Kristi called the doctor in Chicago. "That's when we learned about IVIG [intravenous immune globulin] and off-label uses," said Kristi. "We had a lot of phone conversations with him, and he did a bunch of tests to ensure it was PANDAS and not something else." In fact, Kap had been tested for strep a number of times previously, but the tests always came up negative. But, those doctors, said Kristi, were only testing for the most common types of strep. The doctor in Chicago had him tested for a specific strain of strep that showed unusually high b titers, which indicated PANDAS.

In July, Kap and his parents flew to Chicago for IVIG therapy. His IVIG infusion lasted two days. The bad news: As is often the case for treatments that are prescribed off-label, the insurance company refused to reimburse the family for IVIG treatment. The good news: Kap is now symptom-free. "He didn't wake up the next day and stop coughing," said Kristi. "It happened over time; it was like the pages turning backward." And, according to his doctor, there is no reason to believe Kap will relapse. However, as a precautionary measure, he was given antibiotics after his IVIG therapy.

Kap is now 13. This past year, the energetic young teen won the national tennis championships match in Las Vegas, Nev., as an unseeded player in both singles and doubles. Asked whether his bout with PANDAS may have had anything to do with his success, Kristi said: "I think it's made him a lot more driven. He was always really good in sports. But he feels like he's missed a year, and he's going to make up for it."

As for Kristi, she gives this advice to other parents facing the same situation: "Don't be afraid to find the real root of the problem. Be persistent. You know your own kid. So, just search for the answer until you get what you want."

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).

Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (*see Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur to human immune globulin or components of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra infusion immediately and institute appropriate treatment.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. Hizentra contains ≤50 mcg/mL IgA (*see Description [11]*).

5.2 Thrombotic Events

Thrombotic events have been reported with the use of immune globulin products[1-3], including Hizentra. Patients at increased risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, Factor V Leiden, known or suspected hyperviscosity, and/or those who use estrogen-containing products. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Hizentra at the minimum rate practicable.

5.3 Aseptic Meningitis Syndrome (AMS)

AMS has been reported with use of IGIV[4] or IGSC. The syndrome usually begins within several hours to 2 days following immune globulin treatment. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (≥2 g/kg) and/or rapid infusion of immune globulin product.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of immune globulin treatment has resulted in remission of AMS within several days without sequelae.

5.4 Reactions Reported to Occur With IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

Renal Dysfunction/Failure

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[5] If renal function deteriorates, consider discontinuing Hizentra. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

Hemolysis

Hizentra can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[6-8] Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[9]

Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If these are present after a Hizentra infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Hizentra, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[10] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor Hizentra recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.5 Transmissible Infectious Agents

Because Hizentra is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Hizentra.

Report all infections thought to be possibly transmitted by Hizentra to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.6 Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in ≥5% of study subjects receiving Hizentra, were local reactions (e.g., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, AR rates observed in clinical studies of a product cannot be directly compared to rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

US Study

The safety of Hizentra was evaluated in a clinical study in the US for 15 months (3-month wash-in/wash-out period followed by a 12-month efficacy period) in subjects with PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses included 49 subjects in the intention-to-treat (ITT) population. The ITT population consisted of all subjects who received at least one dose of Hizentra (*see Clinical Studies [14]*).

Subjects were treated with Hizentra at weekly median doses ranging from 66 to 331 mg/kg body weight (mean: 181.4 mg/kg) during the wash-in/wash-out period and from 72 to 379 mg/kg (mean: 213.2 mg/kg) during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

Table 2 summarizes the most frequent adverse reactions (ARs) (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the investigators 15 to 45 minutes post-infusion and by the subjects 24 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments. Local reactions were the most frequent ARs observed, with injection-site reactions (e.g., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

Table 2: Incidence of Subjects With Adverse Reactions (ARs)* (Experienced by 2 or More Subjects) and Rate per Infusion (ITT Population), US Study

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate†) of ARs (n=2264 Infusions)
Local reactions‡	49 (100)	1322 (0.584)
Other ARs:		
Headache	12 (24.5)	32 (0.014)
Diarrhea	5 (10.2)	6 (0.003)
Fatigue	4 (8.2)	4 (0.002)
Back pain	4 (8.2)	5 (0.002)
Nausea	4 (8.2)	4 (0.002)
Pain in extremity	4 (8.2)	6 (0.003)
Cough	4 (8.2)	4 (0.002)
Vomiting	3 (6.1)	3 (0.001)
Abdominal pain, upper	3 (6.1)	3 (0.001)
Migraine	3 (6.1)	4 (0.002)
Pain	3 (6.1)	4 (0.002)
Arthralgia	2 (4.1)	3 (0.001)
Contusion	2 (4.1)	3 (0.001)
Rash	2 (4.1)	3 (0.001)
Urticaria	2 (4.1)	2 (< 0.001)

* Excluding infections.
† Rate of ARs per infusion.
‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

The ratio of infusions with ARs, including local reactions, to all infusions was 1303 to 2264 (57.6%). Excluding local reactions, the corresponding ratio was 56 to 2264 (2.5%).

Table 3 summarizes injection-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).

Table 3: Investigator Assessments* of Injection-Site Reactions by Infusion, US Study

Injection-Site Reaction	Number† (Rate‡) of Reactions (n=683 Infusions§)
Edema/induration	467 (0.68)
Erythema	346 (0.51)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

* 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).
† For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.
‡ Rate of injection-site reactions per infusion.
§ Number of infusions administered during regularly scheduled visits.

Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.

No deaths or serious ARs occurred during the study. Two subjects withdrew from the study due to ARs. One subject experienced a severe injection-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis. Both reactions were judged to be "at least possibly related" to the administration of Hizentra.

European Study

In a clinical study conducted in Europe, the safety of Hizentra was evaluated for 10 months (3-month wash-in/wash-out period followed by a 7-month efficacy period) in 51 subjects with PI who had been treated previously with IGIV every 3 or 4 weeks or with IGSC weekly.

Subjects were treated with Hizentra at weekly median doses ranging from 59 to 267 mg/kg body weight (mean: 118.8 mg/kg) during the wash-in/wash-out period and from 59 to 243 mg/kg (mean: 120.1 mg/kg) during the efficacy period. The 51 subjects received a total of 1831 infusions of Hizentra.

Table 4 summarizes the most frequent ARs (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the subjects between 24 and 72 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments.

Table 4: Incidence of Subjects With Adverse Reactions (ARs)* (Experienced by 2 or More Subjects) and Rate per Infusion, European Study

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=51)	Number (Rate†) of ARs (n=1831 Infusions)
Local reactions‡	24 (47.1)	105 (0.057)
Other ARs:		
Headache	9 (17.6)	20 (0.011)
Rash	4 (7.8)	4 (0.002)
Pruritus	4 (7.8)	13 (0.007)
Fatigue	3 (5.9)	5 (0.003)
Abdominal pain, upper	2 (3.9)	3 (0.002)
Arthralgia	2 (3.9)	2 (0.001)
Erythema	2 (3.9)	4 (0.002)
Abdominal discomfort	2 (3.9)	3 (0.002)
Back pain	2 (3.9)	2 (0.001)
Hematoma	2 (3.9)	3 (0.002)
Hypersensitivity	2 (3.9)	4 (0.002)

* Excluding infections.
† Rate of ARs per infusion.
‡ Includes infusion-related reaction; infusion-site mass; infusion/injection-site erythema, hematoma, induration, inflammation, edema, pain, pruritus, rash, reaction, swelling; injection-site extravasation, nodule; puncture-site reaction.

The proportion of subjects reporting local reactions decreased over time from approximately 20% following the first infusion to <5% by the end of the study.

Three subjects withdrew from the study due to ARs of mild to moderate intensity. One subject experienced injection-site pain and injection-site pruritus; the second subject experienced injection-site reaction, fatigue, and feeling cold; and the third subject experienced injection-site reaction and hypersensitivity. All reactions were judged by the investigator to be "at least possibly related" to the administration of Hizentra.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Hizentra

The following adverse reactions have been identified during postmarketing use of Hizentra. This list does not include reactions already reported in clinical studies with Hizentra (see *Adverse Reactions [6.1]*).

- *Infusion reactions:* Allergic-anaphylactic reactions (including swollen face or tongue and pharyngeal edema), pyrexia, chills, dizziness, hypertension/changes in blood pressure, malaise.
- *Cardiovascular:* Thromboembolic events, chest discomfort (including chest pain)
- *Respiratory:* Dyspnea

General

The following adverse reactions have been reported during postmarketing use of immune globulin products[11]:

- *Infusion reactions:* Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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Bern, Switzerland
US License No. 1766

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA
Based on October 2011 revision

Diagnostic Criteria for PANDAS and PANS

The National Institute of Mental Health has developed a set of criteria for both PANDAS and PANS, the latter of which encompasses the larger class of acute-onset OCD cases.

Criteria for the Diagnosis of PANDAS

1. Presence of OCD and/or a tic disorder
2. Pediatric onset of symptoms (ages 3 years to puberty)
3. Episodic course of symptom severity
4. Association with group A beta-hemolytic streptococcal infection (a positive throat culture for strep or history of scarlet fever)
5. Association with neurological abnormalities (motoric hyperactivity or adventitious movements such as choreiform movements)

Criteria for the Diagnosis of PANS

1. Abrupt, dramatic onset of OCD (including severely restricted food intake)
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of seven categories:
   - anxiety (particularly, separation anxiety)
   - emotional lability (extreme mood swings) and/or depression
   - irritability, aggression and/or severely oppositional behaviors
   - behavioral (developmental) regression (such as baby talk, throwing temper tantrums, etc.)
   - deterioration in school performance
   - sensory or motor abnormalities
   - somatic signs and symptoms, including sleep disturbances, bedwetting or urinary frequency
3. Symptoms are not better explained by a known neurologic or medical disorder such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others

followed by a slow, gradual improvement. And, if they get another strep infection, their symptoms suddenly worsen again with the severity persisting for at least several weeks but sometimes months or longer. Then, the tics or OCD gradually fade away, and they often enjoy a few weeks or several months without problems.[6]

At present, determining whether a child has PANDAS can be based only on a clinical diagnosis.

It's important to note that there does appear to be a genetic susceptibility to PANDAS. Dr. William McMahon, child psychiatrist and geneticist at the University of Utah, studied the broader area of general familial genetic risk. He looked for the presence of OCD and tic disorders in families involved in the current rheumatic fever resurgence in his region. His goal was to see if Tourette disorder (TD) or OCD was associated with the Sydenham chorea criteria for rheumatic fever. In a pilot survey of 100 families, he found almost four times as many Sydenham chorea probands (22%) had relatives with TD/tics or OCD than non-Sydenham chorea rheumatic fever patients (6%). He feels this supports an as-yet unidentified "common genetic risk factor."[7]

A PANS diagnosis also is made entirely on the basis of its history and physical examination. The three criteria developed for a diagnosis of PANS includes: 1) abrupt, dramatic onset of OCD (including severely restricted food intake), 2) concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of seven categories: anxiety (particularly, separation anxiety); emotional lability (extreme mood swings) and/or depression; irritability, aggression and/or severely oppositional behaviors; behavioral (developmental) regression (such as baby talk, throwing temper tantrums, etc.); deterioration in school performance; sensory or motor abnormalities;

and somatic signs and symptoms, including sleep disturbances, bedwetting or urinary frequency and 3) symptoms are not better explained by a known neurologic or medical disorder such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others.[1]

Successful Treatments

The best treatment for acute episodes of PANDAS is to get rid of the strep infection causing the symptoms (if it is still present). This is accomplished with a throat culture to detect the presence of strep bacteria in the throat. If the throat culture is negative, the child should be tested for an occult strep infection, such as a sinus infection or strep bacteria infecting the anus, vagina or urethral opening of the penis. While these latter infections are rare, they have been shown to trigger PANDAS symptoms in some patients. A single course of antibiotics such as amoxicillin, penicillin, azithromycin and cephalosporins will usually get rid of the strep infection.[1]

The best treatment for acute episodes of PANDAS is to get rid of the strep infection causing the symptoms.

While conventional treatments for PANDAS are generally not universally agreed upon, the main treatments include off-label use of common medications used in general practice, including antibiotics, corticosteroids, selective serotonin reuptake inhibitors (SSRIs) and immunomodulatory therapies. When these therapies fail to work, more novel therapies have been used, including intravenous immunoglobulin (IVIG) and plasmapheresis. However, these treatments are not an option for all because of their expense and lack of availability.[8]

Several studies have proved the benefit of these different therapies. In one study, 23 subjects with PANDAS were enrolled in a double-blind, randomized controlled trial and administered antibiotic prophylaxis with penicillin or azithromycin for 12 months. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year prior to entry. Results showed significant decreases in streptococcal infections during the study year compared with the baseline year, as well as significant decreases in neuropsychiatric exacerbations during the study year compared with the baseline year.[9]

In another study, researchers investigated whether plasma exchange or IVIG would be better than a placebo in reducing the severity of neuropsychiatric symptoms. Of the 29 children in the study, 10 received plasma exchange (five single-volume exchanges over two weeks), nine received IVIG (1 g/kg daily on two consecutive days) and 10 received a placebo (saline solution given in the same manner as IVIG). Symptom severity was rated at baseline and at one month and 12 months after treatment. At one month, the IVIG and plasma-exchange groups showed striking improvements in OCD symptoms, and tic symptoms also were significantly improved with plasma exchange. Treatment gains were maintained at one year, with 14 (82 percent) of 17 children much or very much improved over baseline (seven of eight for plasma exchange, and seven of nine for IVIG).[10]

Cognitive behavior therapy (CBT) also has been shown to be safe and minimally invasive. In one study, seven children with OCD of the PANDAS subtype (range 9 to 13 years) were treated in a three-week intensive CBT program conducted at a university clinic. Six of seven children were taking SSRI medication(s) upon presentation. Assessments were conducted at four time points: baseline, pretreatment approximately four weeks later, posttreatment, and three-month follow-up. Six of seven participants were classified as treatment responders (much or very much improved) at posttreatment, and three of six remained responders at follow-up. However, self-reported general anxiety and depression symptoms were not significantly reduced.[11]

There are cautions concerning SSRIs. Because children with PANDAS appear to be unusually sensitive to the side effects of SSRIs and other medications, it is recommended that treatment be prescribed at very small starting doses of the medication and increased slowly enough that the child experiences as few side effects as possible. If symptoms worsen, the dosage should be decreased promptly. However, abruptly stopping SSRIs and other medications may also cause difficulties.[1]

While not a conventional treatment, a literature review of several case studies showed that treatment with tetrabenazine and, subsequently, tonsillectomy, prevented reinfection of strep infections. In one case, an 11-year-old boy who developed PANDAS with severe choreic movements

was initially treated with tetrabenazine 12.5 mg twice daily with remission of the neurological symptoms. Subsequently, the patient underwent tonsillectomy and has been asymptomatic since, with antistreptolysin O titer levels in range.[12]

Preventing Relapses

In many cases, recurrent episodes can occur when there is a resistant strain of the strep infection, when the child contracts another strep infection or even when exposed to strep such as through a family member.

Most children outgrow PANDAS at puberty (ages 12 to 15).

To avoid recurrent episodes, antibiotics are sometimes used as prophylaxis against strep infections. In the antibiotic prophylactic study mentioned previously, the results were successful. However, the use of prophylactic antibiotics is controversial. According to the PANDAS Network, in many of the acute cases profiled on its website, the typical course of antibiotics has not been helpful; the children continue to suffer for months, and symptoms often increase in severity. It is not clear if the acute cases are the exception or the rule.[13]

Most children outgrow PANDAS at puberty (ages 12 to 15). While it's not clear entirely why this occurs, it is known that strep infections are not usually prevalent in children after they have reached puberty. It is suggested that after exposure to multiple strains throughout childhood, a natural immunity to strep infections builds. Families in the PANDAS Network know of many girls who, at the onset of menses, have suddenly stopped having any PANDAS symptoms. And, there are reports of several boys, at age 13 or so, who have stopped having PANDAS symptoms as well.[13]

The Need for Additional Research

Many researchers across the nation have developed hypotheses about the cause of, contributing factors for and treatment of PANDAS. But because PANDAS has been recognized as a rare disease for less than half a decade, it is still unknown just how many children have been stricken with the disorder, possibly putting them at risk of not receiving the treatment they need. Therefore, a great deal of research is yet needed to definitively determine its cause, to find more effective treatments and to put to rest the controversy over whether the disorder is in fact real. ■

PANDAS Resources

- National Institute of Mental Health: **intramural/nimh.nih.gov/pdn/web.htm**
- P.A.N.D.A.S. Network: **pandasnetwork.org**
- Guide to P.A.N.D.A.S. Syndrome: **www.pandas-syndrome.com**
- Behavioural Neuropathy Clinic — Australia: **www.adhd.com.au/PANDAS.htm**

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