In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 99-520V
(E-Filed: May 23, 2007)
To be Published

KHADIJA AALIYAH FRANCIS, a minor, by her mother and natural guardian, DEBORAH VAN BURCH, Petitioner, v. SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, Respondent.	)	Finding of Entitlement; Prior History of Chickenpox Lesions Preceding Varicella Vaccination; Myasthenia Gravis

Clifford Shoemaker, Vienna, VA, for petitioner.

Alexis Babcock, with whom were Peter D. Keisler, Assistant Attorney General, Timothy P. Garren, Director, Vincent J. Matanoski, Acting Deputy Director, and Gabrielle M. Fielding, Assistant Director, Department of Justice, Civil Division, Torts Branch, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless the decisions contain trade secrets or commercial or financial information that is privileged or confidential, or the decisions contain medical or similar information the disclosure of which clearly would constitute an unwarranted invasion of privacy. When a special master files a decision or substantive order with the Clerk of the Court, each party has 14 days within which to identify and move for the redaction of privileged or confidential information before the document's public disclosure. If the special master agrees, upon review of the party's motion, that the identified material falls within the described categories of protected information,

On July 28, 1999, Deborah Van Burch (Ms. Van Burch or petitioner), as mother and natural guardian of Khadija Francis (Khadija), filed a petition pursuant to the National Vaccine Injury Compensation Program[2] (the Act or the Program). 42 U.S.C. §§ 300aa-1 to -34 (2000 & Supp. II 2003). Ms. Van Burch alleges that a varicella vaccination[3] administered on August 15, 1996, to Khadija caused ptosis[4] of her daughter's right eye. See Petition (Pet.) ¶ 3[5]; Petitioner's Exhibit (P. Ex.) 22 ¶ 5 (Affidavit of Ms. Van Burch).

Ms. Van Burch relies on a theory of causation in fact. In support of her theory of causation, Ms. Van Burch has submitted her affidavit, Khadija's medical records, the expert opinion of Carlo Tornatore, M.D., and supporting medical literature. Challenging Ms. Van Burch's theory of causation, respondent has submitted the expert opinion of Thomas Leist, M.D., and a number of medical articles.

During a recorded proceeding on July 12, 2006, the undersigned heard the testimony of the parties' respective experts. The parties have filed post-hearing briefing to address issues that were raised during the hearing. Based on the factual record, the supporting medical literature, and the testimony of the parties' experts and for the reasons more fully addressed in this ruling, the undersigned finds that petitioner is entitled to compensation for the injury that Khadija has sustained.

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the special master shall delete that material from the publicly accessible document.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C.A. § 300aa-10-§ 300aa-34 (West 1991 & Supp. 2002) (Vaccine Act or the Act). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

[3] Varicella is chickenpox. Dorland's Illustrated Medical Dictionary 2008 (30th ed. 2003).

[4] Ptosis is "drooping of the upper eyelid from paralysis . . . ." Dorland's Illustrated Medical Dictionary at 1542.

[5] In her petition, Ms. Van Burch alleges that Khadija received the varicella vaccination on August 16, 1996. Pet. ¶ 3. However, Ms. Van Burch states in her affidavit, and the medical records corroborate, that Khadija actually received the vaccination on August 15, 1996. See P. Ex. 22 ¶ 5 (Affidavit of Ms. Van Burch); P. Ex. 4 at 30 (Khadija's vaccine administration record).

I. Facts[6]

Born on October 4, 1994 by an elective caesarean section, Khadija weighed seven pounds, eleven ounces. Agreed Facts, R's Prehearing Br. at 1; P. Ex. 8. Her Apgar scores[7] at one and five minutes were nine and ten. Id.

Khadija's medical records indicate that prior to receiving the vaccination at issue, she received regular well-child examinations by her pediatrician, Usha Velagapudi, M.D. See generally P. Ex. 4. The medical records also indicate that Dr. Velagapudi treated Khadija for ordinary childhood ailments, including recurrent upper respiratory tract infections and middle ear infections (otitis media). See id. at 19-23, 26.

In May 1995, when Khadija was seven months old, Dr. Velagapudi diagnosed her with "bilateral metatarsus adductus"[8] and prescribed corrective casts for treatment of the condition. P. Ex 4 at 29. During a subsequent examination of Khadija on March 14, 1996, when Khadija was seventeen months old, Dr. Velagapudi noted that Khadija had developed several varicella lesions during the time that her brother had chickenpox. Id. at 26. A little more than four months later, on July 29, 1996, Dr. Velagapudi examined Khadija and diagnosed her with an upper respiratory infection and right otitis media. Id. at 19. Khadija's mother, Ms. Van Burch, reported that Khadija had a several day history of a cough with congestion, a low grade fever, and ear pulling. Id.

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[6] Included in the parties' pre-hearing submissions are certain "[a]greed [u]pon [f]acts," which were proposed by petitioner and set forth in respondent's pre-hearing brief on April 17, 2006. These facts are cited as Agreed Facts (Agreed Facts, R's Prehearing Br. filed 4/17/2006). The undersigned cites to the record for all other facts.

[7] The Apgar score, developed in 1952 by anesthesiologist Virginia Apgar, "is a numerical expression of the condition of newborn, usually determined 60 seconds after birth." Dorland's Illustrated Medical Dictionary 1670; The Apgar Score, http://www.babycenter.com/refcap/3074.html (last visited May 9, 2007). The score reflects a combined numerical measurement of a newborn's appearance (color), pulse (heart rate), grimace (reflex irritability or responsiveness), activity (muscle tone), and respiration. Id.; see also Neil M. Davis, Medical Abbreviations 51 (12th ed. 2005). Each of these five indicators is assigned a number between zero and 2 (2 being the strongest rating), and the numbers are totaled to yield the Apgar score. A perfect score is 10. The Apgar Score, http://www.babycenter.com/refcap/3074.html (last visited May 9, 2007).

[8] Metatarsus adductus is "a congenital deformity of the foot in which the forepart of the foot deviates toward the midline." Dorland's Illustrated Medical Dictionary 1138.

Khadija returned to Dr. Velagapudi seventeen days later, on August 15, 1996, for a follow-up examination of her infected ear. P. Ex. 4 at 18. In the "s[ubjective]" portion of the recorded notes, Dr. Velagapudi wrote that Khadija "has been well since [her] last visit." Id. In the "a[ssessment]" portion of the notes, Dr. Velagapudi wrote, "O[titis]M[edia] resolved." Id. During that office visit, Khadija received a varicella immunization. Agreed Facts, R's Prehearing Br. at 1; P. Ex. 4 at 18. Khadija was a little more than twenty-two months old when she received her varicella vaccination. See Stip. Facts; P. Ex.4 at 18; P. Ex 8.

As reflected in her medical records, two days after Khadija's vaccination, on August 17, 1996, she experienced ptosis of her right upper eyelid and a turning out of her right eye. See P. Ex. 4 at 55. On August 19, 1996, Mandes Kates, M.D., an ophthalmologist, examined Khadija for mild ptosis of the right eye, which showed no swelling or mass. Stip. Facts; P. Ex. 4 at 54. Dr. Kates referred Khadija to a neuro-ophthalmologist for further evaluation. Id.

Two days later, on August 21, 1996, Khadija saw Scott Forman, M.D., a neuro-ophthalmologist. Stip. Facts; P. Ex. 4 at 55. Dr. Forman noted that Khadija had sudden onset of ptosis of the right upper eye lid with "right exotropia,"[9] on August 17, 1996. P. Ex. 4 at 55. On examination of Khadija, Dr. Forman found variable exotropia with variable right upper lid ptosis that completely resolved after a thirty minute period of sleep, but returned almost "[i]mmediately thereafter." Id. at 56. Dr. Forman opined that Khadija had "ocular myasthenia gravis."[10] Id. He recommended obtaining blood tests for anti-acetylcholine receptor antibodies, antinuclear antibodies (ANA),[11] and antistriated

[9] Exotropia is a condition characterized by the "permanent deviation" of the visual axis of one eye away from the visual axis of the other eye. Dorland's Illustrated Medical Dictionary 656. The condition manifests as the turning out of one or both eyes.

[10] Myasthenia gravis is a "disorder of neuromuscular function due to the presence of antibodies to acetylcholine receptors at the neuromuscular junction; characteristics include muscular fatigue and exhaustion tending to fluctuate in severity, without sensory disturbance or atrophy." Dorland's Illustrated Medical Dictionary 1205. Noting his reliance on a sleep test in diagnosing Khadija's condition as myasthenia gravis, Dr. Forman observed that "[t]he sleep test in fact has been found to be more sensitive in cases than using [T]ensilon." P. Ex. 4 at 56.

[11] Antinuclear antibodies are "antibodies directed against nuclear antigens[, the substances that induce a specific immune response] . . . and are frequently found in . . . [autoimmune diseases affecting] connective tissue[s]." Dorland's Illustrated Medical Dictionary 100, 104; see also Mosby's Manual of Diagnostic and Laboratory Tests 91-95.

muscle antibodies.[12] He also recommended performing thyroid function tests and a chest CT scan[13] to rule out the possibility of a thymoma.[14] Id. He strongly suggested a prompt referral to a pediatric neurologist and the prompt institution of corticosteriodal therapy after the completion of Khadija's blood tests "to avoid prolonged lid occlusion" and the impairment of Khadija's vision. Id.

On August 23, 1996, a magnetic resonance imaging (MRI)[15] of Khadija's chest showed a "mild curvature deformity of the thoracolumbar spine." Stip. Facts; P. Ex. 4 at 57. Imaging of Khadija's brain and orbits[16] was normal. P. Ex. 4 at 58-59. Khadija's ANA, anti-striated and anti-acetylcholine antibody titers were negative. Id. at 43. That same day, on August 23, 1996, Dr. Velagapudi, Khadija's pediatrician, noted in Khadija's records "spoke [with] Dr. David--Merck about adverse reaction. Literature search to be done." Id. at 18.

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[12] Antistriated muscle antibody is "a serum antibody titer that has been reported to be positive in 95% of patients with myasthenia gravis and thymoma." Mosby's Manual of Diagnostic and Laboratory Tests 24. A check for the presence of these antibodies in the blood work of a patient often occurs when testing for the presence of anti-acetylcholine receptor antibodies. See id. at 22-24.

[13] A computed tomography (CT) scan is a noninvasive, radiographic procedure that produces an image which may assist in the diagnosis of certain pathological conditions such as tumors, cysts, abscesses, inflammation, and vascular aneurysms. See Mosby's Manual of Diagnostic and Laboratory Tests 1088-1093.

[14] A thymoma is "a tumor derived from the epithelial [(relating to the surface lining)] or lymphoid elements of the thymus." Dorland's Illustrated Medical Dictionary 1909. The thymus "is the site of the production of T lymphocytes." Id. T lymphocytes are "precursor cells" that mature and develop T cell surface markers. Id. T lymphocytes are the cells that are "primarily responsible for cell-mediated immunity." Id. at 1077. The maturation of T cells is regulated by hormones that are produced by the epithelial cells of the thymus. Id. at 1077, 1909. "When activated by antigen, T lymphocytes proliferate and differentiate into T memory cells and the various types of regulatory and effector T cells . . . . " Id. at 1077.

[15] Magnetic resonance imaging (MRI) is a noninvasive diagnostic technique that provides valuable information permitting the evaluation of the head and the spinal cord. See Mosby's Manual of Diagnostic and Laboratory Tests 1189.

[16] An orbit is "the bony cavity that contains the eyeball and its associated muscles, vessels, and nerves." Dorland's Illustrated Medical Dictionary 1320.

Also on August 23, 1996, Cecile Fray, M.D., a pediatric neurologist, evaluated Khadija. P. Ex. 23 at 82; Transcript of July 12, 2006 hearing (Tr.) at 36. On examination of Khadija, Dr. Fray noted right ptosis. P. Ex. 23 at 88. Dr. Fray performed a Tensilon[17] test on Khadija and noted that Khadija's ptosis "improved 100% after administration" of the Tensilon. See P. Ex. 4 at 18; P. Ex. 23 at 88, 118. Dr. Fray concluded that Khadija had ocular myasthenia gravis. P. Ex. 23 at 88. To treat Khadija's condition, Dr. Fray prescribed 15 milligrams per day of prednisone.[18] P. Ex. 23 at 119.

Five days later, on August 28, 1996, Khadija had a follow-up appointment with Dr. Velagapudi. P. Ex. 4 at 18. Dr. Velagapudi noted that Khadija had developed ptosis of one eye with torticollis[19] and that she had been examined at Our Lady of Mercy Medical Center. Id. Her CT scan was normal. Id.

Nearly a month and a half later, on October 10, 1996, Khadija had a follow-up appointment with Dr. Forman. P. Ex. 12 at 22. During the examination, Ms. Van Burch noted "a complete absence of [Khadija's] ptosis." Petitioners' Prehearing Submissions (P. Prehearing Br.) at 3 (citing P. Ex. 12 at 22). She also noted that Khadija no longer had a wandering eye. Id. Further to Ms. Van Burch's observations and because Khadija's exam was normal, Dr. Forman suggested decreasing the dosage of Khadija's prednisone over the next several months. Id.

On December 19, 1996, Khadija saw Dr. Forman again. P. Ex 12 at 20. Dr. Forman noted that Khadija was tapering her prednisone dosage and that she had taken no prednisone for a week. Id. Ms. Van Burch "noted a small variable amount of ptosis." P. Prehearing Br. at 3 (citing P. Ex. 12 at 20). On examination, Dr. Forman found "1-2 mm"

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[17] Tensilon is the trademark name for a solution of edrophonium chloride. Dorland's Illustrated Medical Dictionary 1865. Edrophonium chloride is "an anticholinesterase agent with a duration of action of approximately 10 minutes [that is] used for differential diagnosis and evaluation of treatment requirements in myasthenia gravis." Id. at 590.

[18] Prednisone is "a synthetic glucocorticoid derived from cortisone [that is] administered orally as an antiinflammatory and immunosuppressant in a wide variety of disorders." Dorland's Illustrated Medical Dictionary 1500.

[19] Torticollis is "a contracted state of the cervical muscles" that produces twisting of the neck and a tilting of the head position to one side. Dorland's Illustrated Medical Dictionary 1924.

of right lid ptosis. P. Ex. 12 at 20.

During a follow-up office visit on January 30, 1997, Dr. Forman noted that Khadija had not taken any prednisone for about two months and that she still had variable bilateral ptosis. P. Ex. 12 at 19. Dr. Forman found mild to moderate bilateral ptosis during his examination of Khadija. Id.

Almost three months later, on March 10, 1997, Khadija fainted when a babysitter failed to give her medication to her. P. Ex. 4 at 14. The emergency medical personnel who were called for Khadija took her to the hospital for evaluation. Id. Dr. Velagapudi examined Khadija and noted that she had "mild weakness with wobbling, but was walking fairly well." Id. Additional medical record notes indicated that Khadija had bilateral ptosis with a slightly unsteady gait. P. Ex. 4 at 12.

On March 11, 1997, Khadija's blood work showed that her anti-acetylcholine antibody titer was elevated and that her anti-striated muscle antibody was negative. P. Ex. 15 at 48; see also P. Ex. 23 at 67. The next day, on March 12, 1997, Khadija experienced progressive weakness that required her admission to Westchester Hospital for treatment with intravenous immunoglobin.[20] P. Ex. 4 at 12.

Dr. Forman saw Khadija for a follow-up exam on April 9, 1997. Stip. Facts; P. Ex. 12 at 17. At the time of Khadija's office visit, her medications included prednisone and Mestinon.[21] P. Ex. 12 at 17. Dr. Forman found that Khadija had a marked decrease in her right gaze stability and her ability to gaze upward. Stip Facts; P. Ex. 12 at 17. Additionally, Khadija had symmetric ptosis of both eyes. Id. Dr. Forman noted an

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[20] Intravenous immunoglobin is the administration through the veins of "any of the structurally related glycoproteins that function as antibodies." Dorland's Illustrated Medical Dictionary 912. There are five classes of immunoglobulin, designated respectively as IgA, IgD, IgE, IgG, and IgM. Id. All of these antibodies are produced by white blood cells in the bone marrow, known as B cells. Lauren Sompayrac, How the Immune System Works at 6 (2d ed. 2003). Upon maturation, these antibodies become "antibody factories called 'plasma' B cells." Id. Each antibody binds to a specific antigen, known as a cognate antigen, offering protection against a foreign agent presented in the body. Id.

[21] Mestinon is the trademark name for pyridostigmine bromide, Neil M. Davis, Medical Abbreviations 428 (12th ed. 2005) (cross referenced list of generic and brand name drugs). Mestinon is an "orally active cholinesterase inhibitor [that] prevents the breakdown of acetylcholine by allowing more acetylcholine to accumulate." Mestinon, http://www.mestinon.com (last visited May 16, 2007).

improvement in Khadija's condition, but he felt that Khadija needed the prednisone to maintain her ocular movement and prevent ptosis. Id.

Between June 24, 1997 and June 9, 1998, Khadija received six treatments of intravenous immunoglobin at St. Agnes Hospital. P. Ex. 13 at 11, 32, 50, 61, 87. On February 11, 1999, Michel Slim, M.D., a pediatric surgeon, saw Khadija "in consultation . . . for [her] myasthenia gravis." P. Ex. 4 at 52 (letter dated 2/12/99 from Michel Slim, M.D., to Cecile Fray, M.D.). Dr. Slim recommended that Khadija receive a total thymectomy. Id.

Nearly two weeks later, on February 22, 1999, Khadija was admitted to Westchester Medical Center in New York for the placement of a central line for plasmapheresis.[22] P. Ex. 23 at 50. The additional purposes for Khadija's hospital admission were the weaning from her mestinon, and the tapering of her steroids. Id. Two weeks later, on March 9, 1999, Khadija received a thymectomy. Id.; see also P. Ex. 15 at 10. The central line that had been placed prior to her surgery remained in place following her surgery for additional plasmapheresis "to enable complete weaning of steroids." P. Ex. 23 at 50. Following her surgery, Khadija required hospitalization in May 1999 to receive antibiotic therapy for a sepsis infection associated with her placement line.[23] Id. Khadija's bloodwork during her hospitalization showed a negative varicella zoster titer. P. Ex. 1 at 103.

A little more than three months later, on September 3, 1999, Khadija received DTaP[24] and oral polio vaccinations, but did not receive a scheduled MMR[25] vaccination.

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[22] Plasmapheresis is "the removal of plasma from withdrawn blood, with retransfusion of formed elements into the donor." Dorland's Illustrated Medical Dictionary 1446. The procedure may be performed for therapeutic purposes. Id.

[23] A sepsis infection is an infection resulting from the presence of pathogenic microorganisms or their toxins in blood or tissues. Dorland's Illustrated Medical Dictionary 1681.

[24] The DTaP vaccine is "a combination of diphtheria toxoid, tetanus toxoid, and pertussis vaccine; administered intramuscularly for simultaneous immunization against diphtheria, tetanus, and pertussis." Dorland's Illustrated Medical Dictionary 1998. Diphtheria is an acute infectious disease usually affecting the upper respiratory tract. Id. at 523. Tetanus is an acute infectious disease causing sustained muscular contractions. Id. at 1888. Pertussis, also called whooping cough, is an acute contagious infection of the respiratory tract. Id. at 1410.

P. Ex. 4 at 7. During a follow-up examination five days later, on September 8, 1999, Dr. Fray examined Khadija and noted that she was "asymptomatic." P. Ex. 23 at 45. Khadija, however, returned to Dr. Fray three months later, on December 13, 1999, for an exacerbation of her myasthenia gravis for which Khadija was treated with steroids. Id. at 43.

Dr. Forman examined Khadija fifteen months later on March 22, 2001. P. Ex. 12 at 8-10. Khadija's mother, Ms. Van Burch, reported that Khadija had suffered from intermittent exotropia, but the condition had become constant and was not accompanied by ptosis. P. Ex. 12 at 8. Dr. Forman recommended continued monitoring and a possible course of steroids or surgery if Khadija's condition did not improve. Id.

Khadija saw Dr. Forman on August 19, 2002 and Dr. Fray on August 23, 2002. P. Ex. 23 at 39. Both doctors reported that on examination, Khadija's myasthenia gravis was stable. Id.

Alfred Spiro, M.D., director of the MDA Muscle Diseases Clinic in New York, subsequently examined Khadija on August 20, 2003. P. Ex. 16 at 1-7. The examination was "normal." Id. at 7. Dr. Spiro noted that Khadija had shown "significant improvement" after her thymectomy and that she suffered only "occ[asional] relapses" which were treated with steroids. Id. Dr. Spiro did not recommend any drugs or tests at that time, but he did recommend a follow-up visit in one year. Id.

In February 2006, nearly two and a half years after her visit to Dr. Spiro, Khadija experienced a reoccurrence of ptosis of her right eye. See P. Ex. 34 at 1. On March 8, 2006 and April 21, 2006, Dr. Fray examined Khadija for an "exacerbation of [r]ight eye ptosis." P. Ex. 35 at 2-3. Dr. Forman subsequently examined Khadija on April 17, 2006. P. Ex. 34 at 1. Dr. Forman noted that Khadija had not taken immunosuppressive medications for nearly four years, but after the February 1996 ptosis episode, Khadija began a six-week course of prednisone therapy. Id. At the time of Dr. Forman's

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[25] The measles, mumps and rubella virus (MMR) vaccine is "a combination of live attenuated measles, mumps, and rubella viruses, administered subcutaneously for simultaneous immunization against measles, mumps, and rubella." Dorland's Illustrated Medical Dictionary 1999. Measles is a highly contagious viral disease producing maculopapular skin lesions. Id. at 1108. Mumps is an acute infectious disease usually associated with the painful swelling of one or both parotid glands. Id. at 1181. Rubella, also known as German measles, is an acute infectious disease usually characterized by a slight cold, sore throat and fever, followed by the appearance and generalized spread of a fine pink rash. Id. at 1644.

examination, Khadija was "asymptomatic." Id. He suggested annual follow-up examinations "unless symptoms prompt otherwise." Id. at 2.

Dr. Fray examined Khadija again on August 21, 2006. P. Ex. 35 at 4. She noted that Khadija's myasthenia gravis was "in remission," and she recommended monitoring Khadija for "ocular weakness/fatigue/difficulty breathing." Id. She also recommended a return visit in three months. Id.

II. Discussion

A. Legal Standards

The Vaccine Injury Table lists certain injuries and conditions which, if found to occur within a prescribed time period, create a rebuttable presumption that an administered vaccine caused the injury or condition. 42 U.S.C. § 300aa-14(a). Myasthenia gravis is not a listed injury on the Vaccine Injury Table. Id. Thus, there is no presumption of causation in Khadija's case. Rather, petitioner must prove that the administered varicella vaccine caused Khadija's injury.

A claim for which causation is not presumed under the Act, such as petitioner's claim in this case, is known as an "off-Table" case. To demonstrate entitlement to compensation in an off-Table case, a petitioner must demonstrate by a preponderance of the evidence that the vaccination in question more likely than not caused the injury alleged. 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I) and (II). Petitioner satisfies her burden by demonstrating: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between the vaccination and injury." Althen v. Sec'y of Health and Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005). See also Pafford v. Sec'y of Health and Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006) (stating that "[u]nder this court's precedent, [petitioner] must prove by preponderant evidence both that her vaccinations were a substantial factor in causing the illness, disability, injury or condition and that the harm would not have occurred in the absence of the vaccination") (emphasis added); Shyface v. Sec'y of Health and Human Servs., 165 F.3d 1344, 1353 (Fed. Cir. 1999) (Petitioners "established entitlement to compensation by showing that the [administered] vaccine was both a but-for cause of and a substantial factor in [the vaccinee's] death."); Grant v. Sec'y of Health and Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[Petitioner must] show a medical theory causally connecting the vaccination and the injury.") (citations omitted). A persuasive medical theory offers "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Hines v. Sec'y of Health and

Human Servs., 940 F.2d 1518, 1525 (Fed. Cir. 1991) (citations omitted); Knudsen v. Sec'y of Health and Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994) (same); Grant, 956 F.2d at 1148 (same). A logical sequence of cause and effect requires the support of "[a] reputable medical or scientific explanation" that petitioner may offer "in the form of scientific studies or expert medical testimony." Grant, 956 F.2d at 1148.[26] See also H.R.

[26] The Federal Rules of Evidence do not apply in Program proceedings. See 42 U.S.C. § 300aa-12(d)(2)(B) (stating that the Vaccine Rules "shall . . . include flexible and informal standards of admissibility of evidence"); Vaccine Rule 8(c), Rules of the Court of Federal Claims, Appendix B (providing that "[i]n receiving evidence, the special master will not be bound by common law or statutory rules of evidence"). The United States Court of Federal Claims has held that in Vaccine cases, the Supreme Court's decision in "Daubert[v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594 (1993)] is useful in providing a framework for evaluating the reliability of scientific evidence." Terran v. Sec'y of Health and Human Servs., 41 Fed. Cl. 330, 336 (1998), aff'd, 195 F.3d 1302, 1316 (Fed. Cir. 1999), cert. denied, Terran v. Shalala, 531 U.S. 812 (2000). The Supreme Court in Daubert noted that scientific knowledge "connotes more than subjective belief or unsupported speculation." Daubert, 509 U.S. at 590. Rather, some application of the scientific method must have been employed to validate an expert's opinion. Id. An expert's "testimony must be supported by appropriate validation . . . based on what is known." Id. Factors relevant to evaluating an expert's theory may include, but are not limited to:

> [W]hether the theory or technique employed by the expert is generally accepted in the scientific community; whether it's been subjected to peer review and publication; whether it can be and has been tested; and whether the known potential rate of error is acceptable.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1316 (9th Cir. 1995) (citations omitted), on remand, 509 U.S. 579 (1993); see also Daubert, 509 U.S. at 592-94.

In determining the reliability of a novel proposition, the Supreme Court has offered the following guidance to lower courts:

> [S]ubmission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will be detected. The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Daubert, 509 U.S. at 593-94 (citations omitted).

Rep. No. 99-908, Pt. 1, at 15 (1986), reprinted in 1988 U.S.C.C.A.N. 6344, 6356.

A petitioner need not show that the vaccine was the sole or even the predominant cause of the injury. See Shyface, 165 F.3d at 1353. But, a petitioner bears the burden of establishing "that the vaccine was not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Id. at 1352; see also Pafford, 451 F.3d at 1355 (reiterating that petitioner must prove by preponderant evidence both that the received vaccination was a substantial factor in causing her injury and that the harm would not have occurred in the absence of the vaccination). Petitioner does not satisfy her burden, however, by merely showing a proximate temporal association between the vaccination and the injury. Grant, 956 F.2d at 1148 (quoting Hasler v. United States, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984) (stating "inoculation is not the cause of every event that occurs within the ten day period [following it]. . . . Without more, this proximate temporal relationship will not support a finding of causation")).

_____ In Althen, the Federal Circuit stated that "requiring that the claimant provide proof of medical plausibility, a medically-acceptable temporal relationship between the vaccination and the onset of the alleged injury, and the elimination of other causes – is merely a recitation of this court's well-established precedent." 418 F.3d at 1281. The Federal Circuit added that there is no requirement in the Vaccine Act's preponderant evidence standard that petitioner submit "objective confirmation," such as medical literature, to support petitioner's theory of causation. Id. at 1279. The Federal Circuit explained in Althen that requiring medical literature "prevents the use of circumstantial evidence envisioned by the preponderance standard and negates the system created by Congress, in which close calls regarding causation are resolved in favor of the injured claimants." Id. at 1280 (citing Knudsen, 35 F.3d at 549). The Federal Circuit observed in Althen that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." Id.

Following its decision in Althen, the Federal Circuit issued a decision in Capizzano v. Secretary of Health and Human Services, 440 F.3d 1317 (Fed. Cir. 2006), denouncing the requirement of "either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Id. at 1325. The Federal Circuit found such approach to be "inconsistent with allowing 'the use of circumstantial evidence envisioned by the preponderance standard.'" Id. (citing Althen, 418 F.3d at 1280).

The Federal Circuit's decisions in Althen and Capizzano instruct that a petitioner need not produce particular types of evidence to satisfy her burden of proof. The decisions do not preclude, however, courts from considering medical literature when evaluating expert testimony. As informed by the Supreme Court in Daubert, whether a theory or technique has been subjected to peer review and publication is a "pertinent consideration." 509 U.S. at 593. Accordingly, to establish eligibility for compensation, petitioner must support her theory of causation with a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; see also Grant, 956 F.2d at 1148 ("A reputable medical or scientific explanation must support this logical sequence of cause and effect.").

In Capizzano, the Federal Circuit instructed that a special master avoids error when she gives consideration to "the opinions of [a vaccinee's] treating physicians who [have] concluded that the vaccine was the cause of [the vaccinee's] injury." 440 F.3d at 1326 (citation omitted). The Federal Circuit further instructed that "[t]he fact that the[] physicians' diagnoses may have relied in part on the temporal proximity of [the vaccinee's] injuries to the administration of the vaccine is not disqualifying." Id. (citation omitted).

Under the Act, petitioner's showing of entitlement is rebuttable. Thus, if respondent establishes, by a preponderance of the evidence, that petitioner's injury is "due to factors unrelated to the administration of the vaccine described in the petition," see 42 U.S.C. § 300aa-13(a)(1)(B), petitioner's claim must fail, see Shalala v. Whitecotton, 514 U.S. 268, 270-71 (1995) (stating that under the Vaccine Act, "the Secretary of Health and Human Services may rebut a prima facie case [established by petitioner] by proving that the injury or death was in fact caused by 'factors unrelated to the administration of the vaccine. . . .' [But,] [i]f the Secretary fails to rebut, the claimant is entitled to compensation.) (citations omitted).

B. The Parties' Experts' Opinions of Causation

Two medical experts offered opinions in this case regarding what caused Khadija's myasthenia gravis.

1. Petitioner's Expert's Opinion

Carlo Tornatore, M.D., testified for petitioner. Board certified in neurology, Dr. Tornatore is the current director of the multiple sclerosis and associated autoimmune disorders clinics at Georgetown University in Washington, D.C. Tr. at 8-10. Dr. Tornatore estimates that the clinics under his direction "follow somewhere between 1,500

to 2,000 patients." Id. at 9. Although most of the patients have multiple sclerosis, some of them have myasthenia gravis. Id. About one percent of Dr. Tornatore's patients are pediatric patients. Id. at 35. Dr. Tornatore also serves as the director of the neurology training program. Id. at 9. In that capacity, he annually trains eighteen residents, one pediatric neurology fellow, and approximately two hundred medical students. Id. The undersigned accepted Dr. Tornatore as an expert in neurology. Tr. at 19.

Based on his review of Khadija's medical records, which include notes from pediatric visits dating back to December 12, 1994, just two months after Khadija's birth, Dr. Tornatore testified that "Khadija neurologically did very well up until the time she got the vaccination on August 15, 1996." Id. at 10-11. During office visits on March 25, 1995, April 18, 1995, October 19, 1995, December 12, 1995, and December 22, 1995, Khadija had normal neurological examinations that showed "no deficit" in her central nervous system. See P. Ex. 4 at 21-25.

Nearly two days after she received her varicella vaccination, however, Khadija presented with a "drooping" right eyelid that Dr. Forman, a neuro-ophthalmologist, diagnosed as ocular myasthenia gravis. Tr. at 12. See also P. Ex. 4 at 55-56 (letter dated 8/21/96 from Dr. Forman to Dr. Kates). Dr. Tornatore concurred with the diagnosis of Khadija's condition based on the results of her blood work, a normal CT scan and normal MRIs of her chest and brain, and her positive response to an administered Tensilon test. Id. at 12-13, 15. See also P. Ex. 4 at 57-60 (results of Khadija's chest and brain MRIs and the MRI scan of her orbits); P. Ex. 23 at 88 (administration of Tensilon test). Dr. Tornatore explained that the MRI of Khadija's chest would have revealed the presence of a thymoma, a tumorous growth on the thymus gland located behind the breastplate that is "seen not infrequently in people with myasthenia." Tr. at 15.

Dr. Tornatore testified that myasthenia gravis is "an autoimmune disease" characterized by white blood cells attacking muscle. Id. at 16. Dr. Tornatore explained that, with myasthenia gravis, "the thinking is that there is an antibody or there are other parts of the immune system that are blocking the connection between the nerve and the muscle" that result in muscle weakness. Id. at 13. Dr. Tornatore further explained that Tensilon or edrophonium is a "very specific medication" that increases the presence of neurotransmitters between nerves and the muscles. See id. at 13-14. Neurotransmitters are chemical secretions from nerves that target the postsynaptic receptors in the muscles to permit muscles to contract and to function properly. Id. at 13. Tensilon "keeps that chemical [acetylcholine], the neurotransmitter, between the nerve and the muscle from being broken down." Id. at 14. Dr. Tornatore testified that a positive response to the administration of Tensilon will "pretty much" confirm a diagnosis of myasthenia gravis. Id.

Dr. Tornatore stated that Khadija received an appropriate course of treatment for her condition. Id. at 16-17. She had plasmapheresis, a process that Dr. Tornatore described as a "cleaning [of] the blood . . . [to] remov[e] those antibodies that might actually be causing the problem." Id. at 16. Khadija had a thymectomy, the surgical removal of her thymus to inhibit any continued production by the gland of the "T-cells that are causing the problem." Id. Khadija received prednisone, and she received intravenous immunoglobulin. Id.

Dr. Tornatore stated that Khadija's medical records indicate that in March 1996, she had "three to four varicella lesions" after her brother had chickenpox, a disease that Dr. Tornatore described as "highly, highly contagious." Id. at 43-44. He opined that because Khadija had several varicella lesions five months before her varicella vaccination, her immune system was primed as a result of her exposure to the live virus for a quicker response during her subsequent exposure to the attenuated virus contained in the vaccination. Id. at 20, 24. This anamnestic response or sensitivity response occurs "once the immune system has seen a virus . . . [and] remember[s] it" by invoking, on subsequent exposure, "T-memory cells and T-helper cells . . . to fight [the virus] off even quicker." Id. at 21. Dr. Tornatore stated that once the immune system is "turned on," the white blood cells will attack not only the proteins on the virus, but will also attack certain proteins in the body that "can look like" the proteins on the virus. Id. at 22. This autoimmune process, known as molecular mimicry, is addressed in an article that Dr. Tornatore submitted in support of his opinion, entitled "Virus-Induced Autoimmunity: Potential Role of Viruses in Initiation, Perpetuation, and Progression of T-Cell-Mediated Autoimmune Disease." P. Ex. 30 (Julie K. Olson et al., Virus-Induced Autoimmunity: Potential Role of Viruses in Initiation, Perpetuation, and Progression of T-Cell-Mediated Autoimmune Disease, Vol 14, No. III Viral Immunology 227-250 (2001) (discussing mechanisms by which viral infections can induce autoimmune responses and specifically addressing the mechanisms of molecular mimicry, epitope spreading, direct bystander activation, and the release of cryptic antigens)).

Dr. Tornatore added that Khadija's upper respiratory infection two weeks prior to her vaccination "may have caused the immune system to be boosted." Id. at 29. In support of his proposition, Dr. Tornatore pointed to two case reports of postinfectious myasthenia gravis in children as documented in an article filed in support of respondent's expert's opinion. The first case report involved the development of myasthenia gravis in a child who had chickenpox. Id. at 30; Respondent's Exhibit (R. Ex.) A, Tab 1 (Post infectious Myasthenia Gravis: Report of Two Children, 20 J. Child Neurol. 441, 441 (2005)). The second case report involved a child who had an upper respiratory infection and subsequently developed myasthenia. Tr. at 30; R. Ex. A, Tab 1 at 443. In the first of

the reported cases, a five-year-old boy experienced the onset of symptoms two weeks after he developed chickenpox. R. Ex. A, Tab 1 at 441. In the second of the reported cases, a four year old boy presented with myasthenic symptoms three to four weeks after a viral infection. Id. at 443. In both cases, the acetylcholine receptor binding, blocking and modulating antibodies were negative. Id. at 442-443. Dr. Tornatore opined that Khadija's myasthenic reaction occurred within two days of her varicella vaccination because she had a previous exposure to the virus five months before she received the vaccination. Id. at 33.

Dr. Tornatore addressed the fact that Khadija's blood work on August 21, 1996, six days after her vaccination, was negative for acetylcholine receptor antibodies, id. at 15, 17, but subsequently, in March 1997, was positive for acetylcholine receptor antibodies, id. at 17, 19. He explained that the immune system has two arms, the first of which involves antibodies which are the proteins that can block the receptors in a myasthenic condition. Id. at 17-18. The second arm involves T-cells, the white blood cells that "prime the whole system," and can block the transmission between the nerve and the muscle by a number of different mechanisms. Id. at 18. Dr. Tornatore stated that evaluating whether the T-cells are "in play" in causing disease may be difficult because a patient cannot be tested at a clinical level to determine whether the patient has "T-cells [that are] corrected against myasthenia." Id. at 18.

Of interest to Dr. Tornatore in forming his opinion was an undated notation in Khadija's medical records by Dr. Fray, one of Khadija's treating pediatric neurologists, referring to Khadija's "hip infection related to line sepsis at the time of her [t]hymectomy surgery" and noting:

> She is presently going through her second exacerbation of [o]cular [m]yasthenia. Both of these episodes and at the time of her presentation[,] patient has had live vaccines. Therefore, in view of the temporal relation to the vaccine[,] patient should not receive any further live vaccines.

P. Ex. 23 at 36; see also Tr. at 35-36. Dr. Tornatore stated that Dr. Fray's note indicates that Khadija's "treating physicians felt that the vaccines were the cause of the myasthenia, [and] the vaccinations were what were causing the relapses, and that in fact she should not get anymore live vaccines." Id. at 36.

It is Dr. Tornatore's opinion that "once Khadija was exposed to the varicella [virus] five months prior to vaccination, . . . her immune system [was] primed against it. She subsequently received the vaccination and immediately developed myasthenia." Id. at 33. Dr. Tornatore testified that "[t]here is a biological mechanism to explain it which is

very plausible both in the viral-mediated models as well as the animal models and that the sequence is absolutely right on target for what we would expect to see in somebody who had been previously primed, and so all of that fits together very nicely." Id. at 33-34. He observed that "[t]he antecedent infection that [Khadija] had two weeks prior to the vaccination may have also been a player in that it primed, but if not for the vaccination that would give it specificity and the quickness of it, then it would not have happened." Id. at 34. Dr. Tornatore asserted that Khadija's "antibody status is immaterial" to "understanding the etiology of her myasthenia" because a "cell mediated response [to the chickenpox vaccination] is the root cause of [her] myasthenia." P. Ex. 39 (Supplemental Report of Dr. Tornatore) at 2.

2. Respondent's Expert's Opinion

Thomas Leist, M.D., testified for respondent. Dr. Leist has a doctorate in biochemistry and did postdoctoral work in viral immunology. Id. at 56. He is board certified in neurology. Id. at 57. Currently, he directs the comprehensive multiple sclerosis center at Thomas Jefferson University in Philadelphia, Pennsylvania. Id. at 56. He is also the chief of the neurology division. Id. Additionally, Dr. Leist serves as a faculty member in the academic department teaching medical students, residents, and peers. Id. at 57. He estimates that he personally treats "about 20 to 25 patients" with myasthenia gravis. Id. at 68. The undersigned accepted Dr. Leist as an expert in the field of neurology. Id. at 57.

Dr. Leist did not dispute Khadija's diagnosis of myasthenia gravis. See generally id. at 57-103. He testified that the cause of most cases of myasthenia gravis is unknown. Id. at 58. Addressing the length of time between the administration of an inciting agent and the onset of myasthenic symptoms, he stated that "[n]ormally it takes somewhere around two to three weeks or more for a postinfectious process to take hold" and effect an autoimmune response. Id. at 59. Dr. Leist explained:

> [When an] individual has been exposed to an [inciting] agent, there needs to be a replication of this agent. Afterwards, then there needs to be a response of the immune system to this agent.
>
> If we look at T-cell response, maturation of the T-cell response takes a finite amount of time. Normally against the viral antigen it's probably in the week to two[]week range before you have a T-cell response. If we look both in humans and in animal model system[s] of the viral infection, you have first [the] appearance of an unspecific antibody response, I[g]M which is an acute reactant, and subsequently you have a switch of these antibody

producing cells to producing I[g]G.

> That [is] an antibody, or that's a group of antibodies that needs the help of T-cells in order to allow this switch. So while the first antibody response can occur without T-cell help, the second part[] of the antibody response needs the presence of a specific T-cell response in order to allow this, and so this is a sequence of events that takes time to evolve.

Id. at 59-60.

Referring to the two case reports of myasthenia gravis in pediatric patients following viral illness that he filed in support of his opinion, see R. Ex. A, Tab 1 (Post infectious Myasthenia Gravis: Report of Two Children, 20 J. Child Neurol. at 441), Dr. Leist testified that the cases are important for showing the "timelag between the two events," first the infection and then the myasthenic condition, Tr. at 61. He stated that the case reports are limited to "the description of an event of a viral infection . . . [with] no additional neurological evidence." Id. at 60. Dr. Leist testified that in Khadija's case, the two events of her ear infection at the end of July and the onset of her myasthenia gravis in mid-August are "in a reasonable temporal relationship to each other." Id. at 61-62.

Addressing Dr. Tornatore's theory that Khadija's varicella immunization triggered an immune reaction two days later, Dr. Leist stated:

> Assuming that [the documented lesions in Khadija's medical records] were actually chickenpox lesions, and then afterwards if the child was exposed again to the vaccine. . . [and] if we fast forward to 1999 in May, [nearly three years after Khadija's varicella immunization,] when [her] varicella titers were actually taken, there was no neurologic evidence of varicella antibodies present. . . . [O]bviously the second event[, Khadija's varicella immunization,] was a reasonable amount of the virus that was administered. It was vaccine, and if we assume that the child should have been primed . . . with the first event, [Khadija's noted varicella lesions five months before the immunization,], and the second event is a rechallenge, then . . . the second event would have caused a significant immune . . . response. It is more reasonable than not to expect that in this child there should have been a zero conversion to a varicella-positive state.

Id. at 62-63. But, Dr. Leist observed, that "a laboratory titer taken on [May 27, 1999 indicated that Khadija's] varicella titer was negative. Id. at 65 (citing P. Ex. 1 at 103). Dr. Leist stated that "if in fact there were two exposures to the varicella virus, . . . a wild

type exposure which was acquired by the host and a vaccine exposure[,] [a]nd if this [double] exposure led to a significant off-regulation of antibodies against the acetylcholine receptor, . . . then there also would have had to been a generation of neutral antibodies against the varicella virus." Id. at 66.

Dr. Leist agreed with Dr. Tornatore that, as documented in the medical literature, one "can have myasthenia gravis with or without [the] presence of antibodies against the acetylcholine receptor." Id. at 65. Dr. Leist also agreed that a second exposure to an inciting agent produces "a quicker response," also known as an anamnestic response, that could occur within "a matter of days." Id. at 80. However, absent evidence that Khadija had a positive varicella titer level, Dr. Leist was not persuaded that Khadija's double exposure to the varicella virus, first by live exposure and then by vaccination, triggered her myasthenic condition. Dr. Leist reasoned that "[t]here cannot be a significant T-cell response that made myasthenia and then there was not a significant T-cell response that induced antibodies." Id. at 63.

When asked whether Khadija's antibody level may have been affected by her plasmapheresis, Dr. Leist acknowledged that plasmapheresis, or plasma exchange, "reduces antibodies." Id. at 87. However, based on a study of the effects of regular plasmapheresis on the presence of anti-anthrax antibodies in recipients of anthrax vaccine in which researchers found that "[r]egular plasmapheresis decreased the antibody titers but did not lead to conversion to seronegativity,"[27] Dr. Leist reasoned "that the qualitative result of [Khadija's] test for anti-varicella antibodies was not affected by the plasmapheresis that had occurred one month before." R. Ex. C at 3 (Post-hearing Supplemental Expert Opinion of Thomas Leist, M.D.); see also R. Ex. C, Attach. 2 (Phillip R. Pittman, et al., Protective Antigen and Toxin Neutralization Antibody Patterns in Anthrax Vaccinees Undergoing Serial Plasmapheresis, Vol. 12, No. 6, Clinical and Diagnostic Laboratory Immunology 713, 717 (June 2005)) (observing "a small but consistent and statistically significant reduction in total antibody levels during the period after initial plasmapheresis.").

Dr. Leist also addressed the possibility that Khadija's ear infection and upper respiratory infection weakened her immune system two weeks and that her weakened immune system together with the administered vaccination triggered her myasthenia gravis. Dr. Leist acknowledged that "postinfectious transient immune suppression has

[27] Seronegativity is "the state . . . of showing negative results on serological examination." Dorland's Illustrated Medical Dictionary 1685.

been described for . . . [i]ndividuals . . . [who] are more susceptible to bacterial infections" following the influenza virus. Id. at 66-67. But, Dr. Leist explained,

> If there would have been a significant immune suppression at the time of [Khadija's] vaccination, [making Khadija more susceptible to the attenuated varicella virus contained in the received chickenpox vaccine,] I would have expected . . . other manifestations . . . of . . . significant immune suppression . . . . [such as] fever, chills or a viral exanthema. . . . [N]one of these [manifestations] were observed.

Id. at 67.

It is Dr. Leist's belief that the two day period of time in this case between Khadija's vaccination and the onset of her myasthenia gravis was "enormously short to actually induce a T-cell response." Id. at 73. When questioned whether it is possible to have had two exposures that were so significant that a T-cell response could occur in two days, Dr. Leist responded that "[i]t's potentially possible" and pointed to the swine flu vaccine, which is no longer administered, as "probably the best example." Id. at 100.

Dr. Leist distinguished the swine flu, the administration of which was associated with the onset of Guillain-Barré syndrome[28] in periods of time as short as two days, see P. Ex. 33 at 8 (Lawrence B. Schoenberger, et. al, Guillain-Barré Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1977, Vol. 110, No. 2, Am. J . Epidemiology 105, 112 (1979)), from the varicella vaccine at issue in this case, explaining:

> The swine flu was . . . grown in a cell culture where there was additional antigen being delivered in addition to the flu vaccine or the flu antigen[.] [S]o you had essentially an administration of antigens to which the protein may have already been exposed beforehand.

Id. at 98. Dr. Leist subsequently clarified his statement about an exposure prior to the administration of the swine flu that would have sensitized a swine flu vaccinee stating, "I wouldn't say anything that [the swine flu vaccinees] were exposed to [before they received the swine flu vaccination. Rather,] I'm saying that the swine flu vaccine was not

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[28] Guillain-Barré syndrome is defined as an acute simultaneous inflammation of several peripheral nerves, also known as polyneuritis. Dorland's Illustrated Medical Dictionary 803, 1482.

a highly purified vaccine." Id. at 102. Dr. Leist explained that the swine flu vaccine, like other types of influenza vaccines, was "produced in chicken eggs." See R. Ex. C. at 1 (Post-hearing Supplemental Expert Opinion of Thomas Leist, M.D.). Notable among the theories advanced to explain the association between the swine flu vaccine and the onset of Guillain-Barré syndrome is the theory that the presence of Campylobacter jejuni, a bacterial infection, in the chicken eggs contaminated the vaccine. See R. Ex. C (Supplemental Expert Report of Dr. Leist) at 2 (noting a decreased incidence of Guillain-Barré syndrome after influenza vaccinations following the implementation of careful monitoring procedures and safety interventions); see also http://www.cdc.gov/ncidod/dbmd/diseaseinfo/campylobacter_g.htm (discussing what sort of germ is Campylobacter) (last visited May 21, 2007).

Dr. Leist opined that more likely than not, Khadija would have suffered from myasthenia gravis even if she had not received the varicella immunization. Id. at 67. In support of his opinion, Dr. Leist referenced an exhibit, attached to his filed opinion, entitled "The Natural History and Ophthalmic Involvement in Childhood Myasthenia Gravis at The Hospital for Sick Children," a retrospective study of thirty-four pediatric patients with myasthenia gravis in Toronto, Canada. Id. at 68; see also R. Ex. A, Tab 2 (Paul Mullaney, et al., The Natural History and Ophthalmic Involvement in Childhood Myasthenia Gravis at The Hospital for Sick Children, Vol. 107, No. 3, Ophthamology 504-510 (2000)).

The study addresses three types of myasthenic syndromes that occur in pediatric patients: (1) transient neonatal myasthenia gravis; (2) congenital myasthenic syndromes; and (3) juvenile autoimmune myasthenia gravis. R. Ex. A, Tab 2 (Paul Mullaney et al., The Natural History and Ophthalmic Involvement in Childhood Myasthenia Gravis at the Hospital for Sick Children, 107 Ophthalmology at 504). Cases of transient neonatal myasthenia gravis occur "after transplacental transfer of maternal acetylcholine (AChR) receptor antibodies" and usually resolve before the infants reach two months of age. Id. Congenital myasthenic syndromes "are caused by structural or functional, presynaptic or postsynaptic abnormalities." Id. Most cases of congenital myasthenia gravis "are symptomatic in infancy," but mild cases may appear initially in the second year of life or later. Id. at 505. Because congenital myasthenia gravis is not associated with autoimmune disease, immunosuppressive therapy is not effective in these cases. Id. Cases of juvenile autoimmune myasthenia gravis generally occur between the first and second year of life. Id. Patients with juvenile autoimmune myasthenia gravis are responsive to pharmacological testing with Tensilon. Id.

Referring to the Toronto study addressing the three types of myasthenia gravis that he submitted as respondent's Ex. A, Tab 2, Dr. Leist observed that "in the context of the

Toronto cohort of patients[,] . . . somewhere in the 50[]percent range [of the patients] outgrew the disease." Id. at 91. Although he conceded that no vaccination histories were available for any of the pediatric patients examined in the Toronto series of cases, Dr. Leist stated that Khadija's "time of [myasthenic] onset, [at twenty-two months of age], was about right from [the Toronto] case series[, and] [t]he course of her illness was about that described" for juvenile autoimmune myasthenia gravis, factors which might support a finding that Khadija's condition would have occurred in the absence of her chickenpox vaccination. Id. at 91.

He testified that "the majority of autoimmune diseases are occurring in individuals with a [predisposed] genetic makeup and the appropriate sequence of events." Id. at 74. It is his opinion "in this particular case" that Khadija's myasthenic condition "would have occurred independent of the vaccination." Id.

D. Evaluating the Presented Evidence

Consistent with the Federal Circuit's guidance in Althen, 418 F.3d at 1278, petitioner has set forth a medical theory causally connecting Khadija's varicella vaccination to her claimed injury, myasthenia gravis. Dr. Tornatore offered his expert opinion in support of petitioner's medical theory of causation. He testified that Khadija's varicella lesions five months before receipt of the varicella vaccination and her viral infection two weeks before the vaccination had primed her immune system. He further testified that based on her primed immune system, Khadija experienced a rapid immunological response to her varicella vaccination that triggered an onset of myasthenia gravis. Dr. Tornatore explained that Khadija's response to her double varicella exposures within a five-month period (first, by natural infection and second, by vaccination) was consistent with the immunological phenomenon of an anamnestic response or sensitivity response, which occurs "[o]nce the immune system has seen a virus . . . [and] remember[s] it" by invoking, on subsequent exposure, "T-memory cells and T-helper cells . . . to fight [the virus] off even quicker." Tr. at 21. Dr. Tornatore described how Khadija's varicella vaccination, through the biological mechanism of molecular mimicry, brought about her injury. He explained that molecular mimicry occurs once the immune system is "turned on" and the body's white blood cells attack not only the proteins on the virus, but also attack certain proteins in the body that "can look like" the proteins on the virus. Id. at 22.

Dr. Leist, respondent's expert, acknowledged the plausibility of petitioner's theory noting that Khadija's second exposure to chickenpox by the vaccination was "a rechallenge," id. at 63, if, as documented in Khadija's medical records, the observed lesions five months before her vaccination were in fact chickenpox. Id. at 62. However,

Dr. Leist remained unpersuaded by petitioner's theory of causation in the absence of evidence that: (1) Khadija's noted chickenpox lesions had been verified medically; (2) Khadija's varicella titers had been measured and were found antibody-negative prior to May 1999, nearly three years after Khadija received her vaccination, and (3) Khadija had exhibited fever, exanthema, or other evidence of a significant immunological response after her vaccination. See id. at 62-64, 67.

The pathological markers that Dr. Leist seeks do not exist and, as informed by the Federal Circuit in Capizzano, are not required for petitioner to satisfy her burden of proof under the Program. See Capizzano, 440 F.3d at 1325 (informing that "the presence of pathological markers . . . [is not required] to establish a logical sequence of cause and effect" and quoting its statement in Althen, 418 F.3d at 1280 (emphasis added), that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body").

Of assistance to the undersigned in her evaluation of the significance of Khadija's seronegativity for varicella antibodies is the guidance found in the recommendations issued by the Centers for Disease Control and Prevention (CDC) for prevention of varicella in the Mortality and Morbidity Weekly Report (MMWR) dated July 12, 1996.[29] See http:// www.cdcf.gov/mmwr/preview/mmwrhtml/00042990.htm (MMWR Recommendations and Reports (Prevention of Varicella, Recommendations of the Advisory Committee on Immunization Practices, 45 MMWR (RR-11) (July 12, 1996)). The CDC-issued MMWR "contain[s] in-depth articles that relay policy statements for prevention and treatment with regard to all areas in CDC's scope of responsibility ([including] recommendations from the Advisory Committee on Immunization Practices)." See http://www.cdc.gov/mmwr/mmwr_rr.html (last visited May 22, 2007).

In the MMWR dated July 12, 1996, CDC's Advisory Committee on Immunization Practices (ACIP) issued its recommendations for the prevention of varicella by vaccination. The ACIP reported that "[t]he varicella virus vaccine in the United States is composed of [a particular] strain of live attenuated V[aricella]Z[oster]V[irus]," id. at 6,

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[29] The undersigned afforded counsel and the parties' experts an opportunity to comment upon the undersigned's reliance on the recommendations issued by the Centers for Disease Control and Prevention (CDC) for prevention of varicella in the Mortality and Morbidity Weekly Report (MMWR) dated July 12, 1996. See http:// www.cdcf.gov/mmwr/preview/mmwrhtml/00042990.htm (MMWR Recommendations and Reports (Prevention of Varicella, Recommendations of the Advisory Committee on Immunization Practices, 45 MMWR (RR-11) (July 12, 1996)).

and that the measured "seroconversion rate . . . after one dose of vaccine among 6,889 susceptible children [between] 12 months [to] 12 years of age [has been] demonstrated to be 97%," id. The ACIP further reported that antibody levels "measured yearly for 4 years after vaccination [were] consistently high . . . in children vaccinated [between 12-36 months and between 48-144 months] of age although the numbers of children tested decreased considerably as the length of time since vaccination increased." Id. The reported period of effective immunization following the varicella virus vaccination is "7-10 years." Id. at 8. Within that period of time, the vaccination "provides 70%-90% protection against infection." Id. The ACIP recommended the varicella vaccination for "all susceptible children by their 13th birthday," and noted that the vaccine "may be administered at any time after 18 months of age." Id. at 11.

The ACIP noted that "[p]atients at high risk for severe disease and complications [resulting from varicella infection] . . .include . . . immunocompromised persons of all ages." Id. at 3. The ACIP further noted that "[b]ecause the rash [indicative of varicella infection] is distinctive and subclinical cases rarely occur, most parents know if their child has had varicella." Id. at 4.

As reported by the ACIP in the MMWR dated July 12, 1996, the observed seroconversion rate of 97% after one dose of varicella vaccination would appear to support Dr. Leist's expectation that after receiving the vaccination, the vaccinee would have positive antibodies for varicella. While the reported seroconversion rate after a single dose of varicella vaccination was high in most cases, implied in the less than one hundred percent rate of seroconversion is the existence of the apparently rare cases in which seroconversion fails to occur. This phenomenon, inferred from the ACIP's MMWR dated July 12, 1996, would appear to lend support to a finding in this case that Khadija's failure to show a positive seroconversion after the receipt of her varicella vaccination does not necessarily compromise her Program claim. See, e.g., Werderitsh v. Sec'y of Health and Human Servs., No. 99-310V, 2006 WL 1672884, at *25 (Fed. Cl. Spc. Mstr. May 26, 2006) (declining to conclude that a petitioner's "failure to produce antibodies" to the received vaccine "means [the vaccinee] did not have another type of mechanism unrelated to antibody production in response to [the received] vaccine that caused or exacerbated her [condition]" when expert testimony established that the condition could have been caused by a process other than an antibody-mediated process).

1. Applying the Althen Standard

Here, petitioner's expert witness, Dr. Tornatore, has advanced a medical theory of vaccine causation that is based on a plausible biological mechanism which finds support in the medical literature. Respondent's expert witness, Dr. Leist, does not dispute the

plausibility of the proposed biological mechanism although, in the absence of varicella antibodies, he does not believe that Khadija's vaccination caused her injury.

Khadija's medical records reflect a consistent diagnosis of her condition as myasthenia gravis. As addressed in medical literature, myasthenia gravis (MG) is "an autoimmune disease that results when self-reactive antibodies bind to the receptor for . . . [the] neurotransmitter, acetylcholine. When the message that is normally carried by acetylcholine from nerve to muscle is not received (because the antibodies interfere with its reception), muscle weakness and paralysis can result." Lauren Sompayrac, How the Immune System Works at 102 (2d ed. 2003); see also P. Ex. 27 (Angelo A. Manfredi, et al., T Helper Cell Recognition of Muscle Acetylcholine Receptor in Myasthenia Gravis: Epitopes on the γ and δ Subunits, 92 J.Clin Invest. 1055, 1055 (August 1993) (explaining that a myasthenic condition results when an autoimmune response against the acetylcholine receptor (AChR) occurs in a muscle)); Respondent's Exhibit (R. Ex.) A, Tab 1 (Postinfectious Myasthenia Gravis: Report of Two Children, 20 J. Child Neurol. 441, 441 (2005) (describing myasthenia gravis as "an autoimmune neuromuscular disorder")). An acetylcholine receptor is the molecular structure within a muscle cell that binds the neurotransmitter acetylcholine, a chemical substance that is present in the nerve terminations in striated muscles, to permit proper muscle function. See Dorland's Illustrated Medical Dictionary 13, 1260, 1593; see also Tr. at 13 (testimony of Carlo Tornatore, M.D., petitioner's expert). Anti-acetylcholine receptor antibodies are circulating antibodies that act against the acetylcholine receptors at myoneural[30] junctions. See Dorland's Illustrated Medical Dictionary 100.

High titers[31] of anti-acetylcholine receptor antibodies "are demonstrable in about 85 percent of myasthenia gravis patients." Id. In a reported study of twenty-two myasthenic patients and ten healthy controls, however, researchers found a "poor correlation" between antibody titer level and disease severity. P. Ex. 27, Attach. 2 (Angelo A. Manfredi, et al., T Helper Cell Recognition of Muscle Acetylcholine Receptor in Myasthenia Gravis: Epitopes on the γ and δ Subunits, 92 J. Clin Invest. at 1059). The researchers also found that "[s]everal patients with little or no detectable anti-AChR antibody . . . had detectable T cell responses." Id. The researchers reported that some of the cases of "antibody-negative M[yasthenia]G[ravis]" in the study suggested that an

[30] Myoneural means "pertaining to the nerve terminations in muscles." Dorland's Illustrated Medical Dictionary 1215.

[31] A titer is the "quantity of a substance required to produce a reaction with a given volume of another substance." Dorland's Illustrated Medical Dictionary 1916.

"[auto]immune anti-AChR response" was occurring. Id. at 1063. Other researchers have postulated that "[i]mmunological cross-reactivity between viral or bacterial antigens and normal protein constituents of the host may be involved in [the] development of autoimmune diseases, including M[yasthenia]G[ravis], because microbial proteins and human autoantigens contain identical or similar sequence segments, which may form cross-reacting epitopes." P. Ex. 27, Attach. 4 (Maria P. Protti, et al., Myasthenia Gravis: CD4+ T Epitopes on the Embryonic γ Subunit of Human Muscle Acetylcholine Receptor, 90 J.Clin. Invest. 1558, 1565 (October 1992)).

The medical literature also indicates that researchers have associated the onset of a myasthenic condition with several precipitating factors. Myasthenia gravis "is frequently associated with abnormalities of the thymus gland . . . . Much less often, the disorder is [deemed to be] precipitated by other factors, including medications and infections." R. Ex. A, Tab 1 (Postinfectious Myasthenia Gravis: Report of Two Children, 20 J. Child Neurol. 441, 441 (2005)). In this case, petitioner's expert witness, Dr. Tornatore, testified that the precipitating factors for Khadija's condition were her prior exposure to the varicella virus, her upper respiratory infection two weeks before her vaccination, and her varicella vaccination. Dr. Tornatore opined that not only was the vaccination a substantial factor in causing Khadija's condition, "but if not for the vaccination . . . [her myasthenia gravis would not have happened." Tr. at 34. Consistent with the requirements articulated in Althen, Dr. Tornatore offers, on petitioner's behalf, a medical theory of a plausible biological mechanism causally connecting Khadija's vaccination to her injury.

Although respondent's expert, Dr. Leist, testified that Khadija's condition resulted from the upper respiratory infection she had two weeks before her vaccination, a factor unrelated to her vaccination, at least one of Khadija's treating neurologists, specifically, Dr. Fray, was sufficiently concerned regarding the causal impact of Khadija's vaccination, that Dr. Fray discouraged any further administration of live vaccines to Khadija. See P. Ex. 23 at 36. Dr. Fray's concern that Khadija not receive any more live vaccines was one of the considerations influencing the opinion of petitioner's expert, Dr. Tornatore, and the concern expressed by Dr. Fray militates in favor of a finding that Khadija's vaccination was not an insubstantial factor in the development of her condition. Based on the medical records and expert testimony produced in this case, the undersigned is persuaded that Khadija's injury is causally connected to the chickenpox vaccination that she received.

As further required by the Federal Circuit in Althen, petitioner has presented a logical sequence of cause and effect showing that the vaccination was the reason for the injury. Althen, 418 F.3d at 1278. The evidence demonstrating the plausibility of

petitioner's theory also demonstrates a logical causal sequence. Additionally, petitioner has shown a proximate temporal relationship between the vaccination and the onset of Khadija's myasthenic symptoms. See Althen, 418 F.3d at 1278. Accordingly, petitioner has established, by a preponderance of the evidence, that her myasthenia gravis is causally connected to her varicella vaccination.

III. CONCLUSION

For the foregoing reasons, the undersigned finds that petitioner has established, by a preponderance of the evidence, that her myasthenia gravis is causally connected to her varicella vaccination. Accordingly, petitioner is entitled to reasonable compensation. **On or before June 1, 2007,** the parties shall contact the court to schedule a status conference to address further proceedings in this case to resolve the issue of damages.

IT IS SO ORDERED.

s/Patricia E.Campbell-Smith
Patricia E. Campbell-Smith
Special Master