In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 10-351V
May 30, 2014
To be Published

MADISON TURKUPOLIS,	*	
	*	
Petitioner,	*	
	*	
v.	*	HPV vaccine (Gardasil);
	*	neurocardiogenic syncope;
SECRETARY OF HEALTH	*	basilar migraine
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Ronald C. Homer, Boston, MA, for petitioner.
Voris E. Johnson, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

On June 7, 2010, Jill Turkupolis filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa–10-34 (2006), alleging that the second administration of human papillomavirus vaccine ("Gardasil") on September 10, 2007, caused her daughter Madison unspecified neurological injuries. On November 4, 2010, petitioner filed an amended petition alleging unspecified neurological injuries with detailed descriptions of the contents of medical records.

Madison was a minor at the time her mother filed the petition and amended petition. Madison reached her majority on December 2, 2012. On December 3, 2012, petitioner moved to

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would constitute a clearly unwarranted invasion of privacy. When such a decision is filed, petitioner has 14 days to identify and move to redact such information prior to the document's disclosure. If the special master, upon review, agrees that the identified material fits within the categories listed above, the special master shall redact such material from public access.

amend the caption to reflect that Madison was now the petitioner in this case. By an Order dated December 4, 2013, former Special Master Daria J. Zane, who presided over this case, granted petitioner's motion.

Special Master Zane held a hearing in this case on April 24, 2012 (followed by a transcript filed on May 30, 2012) and December 13, 2012 (followed by a transcript filed on January 15, 2013). Dr. Svetlana Blitshteyn testified for petitioner. Dr. John MacDonald testified for respondent. Both are neurologists.

On May 24, 2013, the parties filed simultaneous post-hearing briefs. On August 2, 2013, the parties filed simultaneous responsive briefs. At the end of August, Special Master Zane retired.

On September 23, 2013, this case was transferred to the undersigned.

On October 24, 2013, petitioner moved for leave to file newly discovered evidence consisting of Exhibit 47, an article petitioner's expert Dr. Blitshteyn wrote on postural tachycardia syndrome ("POTS") following human papillomavirus vaccination, which petitioner also filed on October 24, 2013. Ex. 47. Respondent did not respond to petitioner's motion. On November 14, 2013, the undersigned granted petitioner's motion for leave to file.

On November 21, 2013, the undersigned held a telephonic status conference to discuss the undersigned's view of the case and to inquire if the parties were willing to engage in settlement negotiations. The undersigned offered the parties the opportunity to have a new hearing since they now had a new special master presiding over the case. The parties declined the offer to have a new hearing.

On December 4, 2013, the undersigned held a telephonic status conference in which the parties expressed the unlikelihood of settlement. The undersigned ordered petitioner's expert Dr. Blitshteyn to answer eight questions in a supplemental report due December 18, 2013.

On January 17, 2014, petitioner filed a status report stating settlement was not feasible.

After three extensions of time, on April 4, 2014, petitioner filed the supplemental expert report of Dr. Blitshteyn as Exhibit 48. The case is now ready for decision.

FACTS

Madison was born on December 2, 1994.

On June 23, 2006, Madison's blood pressure was 138/70. Med. recs. Ex. 1, at 2. She was going to travel to Latvia. Id.

On June 28, 2006, Madison's mother called her pediatrician's office. Id. at 3. She reported that Madison's blood pressure was checked at her grandmother's house on June 25, 2006, and she had a systolic blood pressure of 117 and an unknown diastolic blood pressure. Id. Madison's pediatrician advised her mother to have Madison visit the pediatrician or call the pediatrician with a specific, accurate blood pressure reading prior to Madison's departure to Latvia on June 30, 2006. Id. The pediatrician would recheck Madison's blood pressure when she returned from her trip to Latvia. Id.

On June 29, 2006, Madison's mother phoned the pediatrician to say that Madison's blood pressure readings that day were 121/60 with a pulse of 75, and 112/56 with a pulse of 75. Id.

On April 30, 2007, Madison's father called the pediatrician to say that Madison fell over a fence on April 29 and hit the top of her head. Id. at 4. She did not vomit, but she was lightheaded and dizzy. Id. She had nausea and headache and went to the emergency room at St. Vincent's Children's Hospital. Id. Her chief complaint was head injury, headache, and nausea. Med. recs. Ex. 23, at 126. She had no recall of the events. Id.

On May 3, 2007, Madison's headache persisted without relief. Med. recs. Ex. 1, at 4. She had had it for four weeks, and it was more intense now. Id. She was seen in the emergency room, where she had a negative CT scan of her head except for extensive sinus inflammation. Id. She was prescribed Augmentin.[2] Id.

On July 2, 2007, Madison received her first human papillomavirus vaccination. Id. at 4.

On September 10, 2007, Madison received her second human papillomavirus vaccination. Id.

On September 16, 2007, Madison had a CT scan of her brain because of loss of consciousness, neck pain, and headache. Id. at 28. The CT scan was negative. Id.

On September 18, 2007, Madison saw Dr. Leonard A. Steinberg, a cardiologist. Her blood pressure was 125/84. Id. at 21. Dr. Steinberg diagnosed Madison with peri-exertional syncope (fainting from exertion). Id. at 22.

On September 19, 2007, Fishers Emergency Medical Services treated Madison for general weakness, loss of consciousness, palpitations, and syncope. Med. recs. Ex. 16, at 1, 3. Her blood pressure was 135/83. Id. at 3.

---

[2] Augmentin is "trademark for combination preparations of amoxicillin and clavulanate potassium." Dorland's Illustrated Medical Dictionary 179 (32d ed. 2012) [hereinafter Dorland's]. Amoxicillin is an antibiotic. Id. at 65. Clavulanate potassium treats infections. Id. at 370.

On October 4, 2007, Madison's mother phoned the pediatrician, saying Madison's ECHO, EKG, treadmill exercise test, and cardiac MRI were normal. Med. recs. Ex. 1, at 5. Madison had had some dizziness, but she was not passing out. Id. The pediatrician recommended no further sports until he cleared her. Id. He noted that Madison may have some kind of vasovagal[3] problem. Id.

On October 12, 2007, Madison saw Dr. Steinberg, complaining of exertional syncope and dizziness. Id. at 19. Her blood pressure was 136/80. Id. Dr. Steinberg concluded Madison did not have cardiac problems. Id. at 20. He diagnosed Madison with exertional syncope and dizziness. Id. at 19.

On October 23, 2007, Madison saw Dr. David Harsha, complaining of shortness of breath beginning within the first five or ten minutes of exercise. Med. recs. Ex. 21, at 1. Symptoms could become severe to the point of her almost collapsing, especially at the end of her cross-country race. Id. Symptoms always occurred during running and not soccer, but the problem resolved within five or ten minutes of stopping exercise. Id. Dr. Steinberg had prescribed Florinef,[4] after which she had no further syncopal or presyncopal episodes, but she still had breathing difficulties. Id. She was currently excelling in school subjects and pushed herself very hard in school and sports. Id. at 2. Dr. Harsha recorded Madison's blood pressure as 136/84. Id. He thought her symptoms were suggestive of vocal cord dysfunction but could represent irritable larynx syndrome, breath-holding, or anxiety/stress related to athletic participation. Id. at 3. Her presyncopal episodes were most consistent with neurocardiogenic syncope, which appeared to be responding to Florinef. Id. Dr. Harsha had Madison do a reflux symptom index, and she scored 15. Anything above 10 suggests clinically significant gastroesophageal reflux. Id.

On December 31, 2007, Madison received her third human papillomavirus vaccination. Med. recs. Ex. 1, at 5.

On January 24, 2008, Madison saw Dr. Steinberg. Id. at 16. She said that over the last several weeks, she had episodes of dizziness and spacing out while standing. Id. She did not

---

[3] "Vasovagal" means "vascular and vagal." Dorland's at 2027. "Vagal" pertains to the vagal nerve. Id. at 2018. See note 5 infra for the definition of "vasovagal syndrome."

[4] Florinef is "trademark for preparations of fludrocortisone acetate." Dorland's at 718. Fludrocortisone acetate is "the acetate salt of a synthetic steroid with potent mineralocorticoid and high glucocorticoid activity, used in replacement therapy for primary or secondary adrenocortical insufficiency in Addison disease and for the treatment of salt-losing adrenogenital syndrome . . . ." Id. at 719. Mineralocorticoids affect "the regulation of electrolyte and water balance." Id. at 421. Glucocorticoids "participate in the maintenance of arterial blood pressure." Id. at 789. Florinef has a "marked effect on sodium retention" as well as on water retention. www.drugs.com/pro/florinef.html (last visited April 30, 2014). Some of its adverse effects may be "vertigo, headache, and severe mental disturbances" as well as "syncopal episodes." Id.

have associated syncope. Id. She continued to have fatigue and pallor with prolonged exercise. Id. There was a family history of hypertension. Id. Dr. Steinberg diagnosed Madison with likely vasovagal syncope[5] and elevated blood pressure (140/81), but no structural heart disease. Id.

On March 10, 2008, Madison saw Dr. Anup Patel at the Riley Hospital for Children, with complaints of syncope and transient alterations in awareness. Id. at 13. Madison's syncopal episodes began in September 2007 when she was doing cross-country running. Id. She developed episodes of dizziness and lightheadedness. Id. She became confused and did not know where she was. Id. She had two episodes where she passed out. Id. Madison saw her cardiologist Dr. Steinberg, who diagnosed her with vasovagal syncope. Id. Madison started on Toprol[6] but had adverse effects. Id. Dr. Steinberg changed her medication to Florinef. Id. Initially, her episodes decreased, but they returned and were frequent. Id. She began taking Prozac at the end of January 2008, but there was no change in the episodes. Id. She would go two to three days without an episode, but on most other days, she had two to three episodes. Id. The episodes occurred with and without exercise. Id. One morning, she had a headache and then later had an episode at school that lasted forty minutes. Id. Prior to the episode, Madison began to sweat. Id. She then became very confused, did not recognize her teacher or classmates, could not talk, was scared, cried, and her eyes dilated. Id. She was not tired afterwards. Id. During the episodes, she became dizzy and clumsy. Id. Her episodes generally lasted five minutes. Id. Dr. Patel's differential diagnosis was syncope, seizures, and psychogenic[7] causes. Id. at 14.

Also on March 10, 2008, Madison saw the Child Psychiatry Consult Team composed of Dr. David Dunn, a staff psychiatrist and neurologist, at Clarian Health. Med. recs. Ex. 2, at 25. Dr. Dunn diagnosed her with conversion disorder,[8] rule out epilepsy. Id. Dr. Dunn recommended she discontinue Prozac if she and her family did not feel it was effective. Id.

---

[5] "Vasovagal syncope" is "a transient vascular and neurogenic reaction marked by pallor, nausea, sweating, bradycardia, and rapid fall in arterial blood pressure which, when below a critical level, results in loss of consciousness and characteristic electroencephalographic changes. It is most often evoked by emotional distress associated with fear or pain." Dorland's, at 1818.

[6] "Toprol-XL is approved for the treatment of high blood pressure." www.toprol-xl.com (last visited April 30, 2014).

[7] "Psychogenic" means "produced or caused by psychological factors." Dorland's, at 1549.

[8] "Conversion disorder" is "a mental disorder characterized by conversion symptoms (loss or alteration of voluntary motor or sensory functioning suggesting physical illness, such as seizures, paralysis, dyskinesia, anesthesia, blindness, or aphonia) having no demonstrable physiological basis and whose psychological basis is suggested by (1) exacerbation of symptoms at times of psychological stress, (2) relief from tension or inner conflicts (primary gain) provided by the

On March 14, 2008, Madison had a brain MRI, which was normal. Med. recs. Ex. 1, at 15.

From March 17–18, 2008, Madison saw Dr. Michael W. Risinger for a prolonged video EEG monitoring, with a normal result. Med. recs. Ex. 2, at 134. While Madison experienced mild disorientation lasting five to ten minutes during the monitoring, no electrographic ictal[9] changes were seen during that event. Id. Dr. Risinger opined that Madison's confusional episodes were possibly of psychogenic origin, perhaps related to stress. Id. at 135.

On March 27, 2008, Dr. Dunn, a psychiatrist, spoke with Madison's family. Med. recs. Ex. 8, at 2. Her family was not interested in having counseling. Id.

On July 16, 2008, Madison's mother filled out a VAERS (Vaccine Adverse Event Reporting System) report, noting that all of Madison's symptoms disappeared by May 8, 2008. Med. recs. Ex. 26, at 1.

On August 29, 2008, Madison saw Dr. Erica Leazenby, complaining of congestion, ear pressure, and dizziness. Med. recs. Ex. 24, at 1. She had experienced congestion and itchy eyes for two weeks. Id. She was now experiencing dizziness-near vertigo during activity and rest. Id. She had similar symptoms every fall. Id. Her mother has allergies. Id. Madison was excelling in school, pushing herself very hard in school and sports. Id. at 2. She was a straight A student and exercised regularly. Id. Dr. Leazenby diagnosed Madison with allergic rhinitis. Id.

On September 14, 2009, Madison saw Dr. Leazenby, complaining of dizziness two weeks earlier while playing soccer. Id. at 3. She also had nasal congestion. Id. Madison stated she had vertigo daily during soccer practice with episodes lasting five to fifteen minutes. Id. She denied syncope or lightheadedness. Id. She took Claritin regularly but felt her allergies were still severe. Id. On examination, Madison had clear rhinorrhea and boggy mucosa. Id. at 4. Dr. Leazenby diagnosed Madison with peripheral vertigo and allergic rhinitis. Id. Dr. Leazenby thought the vertigo might be related to undertreated allergies. Id. at 5.

On October 12, 2009, Madison saw Dr. Jennifer A. Zimmer, a neurologist. Med. recs. Ex. 14, at 34. Her last visit to the clinic was in March 2008, when she was having frequent episodes of transient alteration of awareness that discontinued in May 2008. Id. A definitive diagnosis was not made. Id. Her episodes consisted of dizziness, clumsiness, and confusion. Id. Her more recent episodes began in September 2009 when she first noticed flashing lights lasting for a few minutes while she became dizzy. Id. Her vision was out of focus, and her ears might

---

symptoms, or (3) secondary gains (support, attention, avoidance of unpleasant responsibilities) provided by the symptoms." Dorland's, at 549.

[9] "Postictal" means "occurring after a seizure or sudden attack." Dorland's, at 1502.

or might not pop. Id. Her left hand occasionally twitched during these episodes. Id. She was able to respond but had a dazed appearance. Id. Madison noted a headache occurred with these episodes over the past two weeks. Id. She did not have nausea, photophobia, or phonophobia. Id. Her episodes lasted approximately thirty minutes. Id. She would then blink several times at the end and then be responsive again. Id. She recalls these episodes and what happens during them. Id. They can occur two to three times a day. Id. They occasionally occur on weekends. Id. Initially, they occurred primarily during sports activities, but they now also occur at rest. Id. She can be sitting or standing when they happen. Id. Madison is a good student and active in sports, including soccer and basketball. Id. Madison has seasonal allergies. Id. Her blood pressure was 147/70. Id. Dr. Zimmer considered seizures and a migraine variant as differential diagnoses. Id. at 35.

Madison had an ambulatory EEG monitor from October 20–23, 2009, which Dr. Zimmer interpreted as abnormal. Med. recs. Ex. 11, at 23. Dr. Zimmer wrote that Madison had partial-onset seizures in the left central head region, which spread to the parietal region. Id.

On November 4, 2009, school nurse Ann O'Hauer, RN, noted Madison was on new seizure medication (Keppra) and was having post-seizure effects. Med. recs. Ex. 10, at 22.

From December 7–11, 2009, Madison was admitted at Indiana University Hospital, where a video EEG unit recorded no seizure episodes. Med. recs. Ex. 12, at 1.

On December 17, 2009, Dr. Zimmer told Madison's parents that what while the ambulatory EEG initially raised concern of possible partial-onset seizures, further review showed it likely represented artifact over the left hemisphere. Med. recs. Ex. 14, at 30. This is why she was referred for the 4-day video EEG. Id. Dr. Zimmer noted that Madison's parents did not want further psychiatric evaluation of Madison because they did not feel her events were due to a psychological basis. Id. Dr. Zimmer noted that Madison might be having atypical or complicated migraines, which would explain why she improved with Topamax. Id.

A Health Care Plan for the school year of 2010–2011 recounts Madison having episodes of dizziness, staring off, and being unaware of her surroundings in 2008. Med. recs. Ex. 31, at 13. She seemed only aware of her name and was unable to give information about date, time, or place. Id. This would happen three to four times a day and last from fifteen to forty-five minutes. Id.

On September 29, 2010, Madison saw Dr. Robert P. Nelson, Jr., at the Indiana University Hospital Pediatric Immunodeficiency Clinic. Med. recs. Ex. 17, at 6. She was referred by Dr. Zimmer to rule out the possibility of Madison having a primary immune deficiency. Id. Madison had a suspected episode of shingles. Id. She had 100 episodes of transient altered awareness over the prior three years. Id. Madison went into a state of mind in which she did not recall what was going on. Id. She did not have actual jerky movements or seizure activity. Id. These episodes lasted five to forty-five minutes. Id. A physician had never observed these episodes.

Id. They did not involve fever or any classic allergic symptoms. Id. Lately, the episodes had occurred more often during soccer games. Id. Dr. Nelson noted that the reasons for her episodes were unclear to him. Id. Madison was on Topamax, Zyrtec, and Zantac. Id. at 7. Dr. Nelson wrote that Madison had a relatively normal childhood and a lack of clinical problems until relatively recently. Id. He noted that this would militate against a broad-based primary immunodeficiency. Id. at 8.

On October 1, 2010, the nurse at Madison's high school received a telephone call from Madison's mother, saying that Madison had a head injury while playing soccer on September 27, 2010, when she banged heads with another soccer player during a game. Med. recs. Ex. 31, at 37. Madison initially had a knot on her head and was dizzy, confused, and nauseated. Id. She was better on September 30, but had a headache on September 29 and 30. Id.

On October 27, 2010, Madison saw Dr. Nelson for a follow-up visit. Med. recs. Ex. 36, at 4. She was experiencing atypical episodes of altered awareness and had a rash on her lower back on more than one occasion, raising the concern of a herpes zoster infection. Id. Her Epstein-Barr virus titers revealed a pattern consistent with recent infection. Id. Dr. Nelson's impression was that Madison had an atypical symptom complex associated with elevated IgM, but no other signs of immune dysregulation. Id. He did not recommend Madison return to see him. Id. at 5.

On April 25, 2011, Madison saw Dr. Zimmer. Med. recs. Ex. 32, at 5. Madison had not had any episodes since late September 2010. Id. She was running eight miles per week and participating in basketball. Id. She was going to work at concessions at a baseball facility in the summer and was participating in soccer. Id. She continued to do well in school. Id.

On August 29, 2011, Madison saw Dr. Zimmer. Id. at 3. Madison had been symptom-free for one year. Id. at 4.

On December 8, 2011, Madison saw Dr. Zimmer. Id. at 1. Madison had a headache and a lump at the back of her head. Id. She had had an upper respiratory infection for the past several days. Id. She had sore throat, congestion, and headache. Id. She no longer had headache. Id. Dr. Zimmer considered that she could have a reactive lymph node from a recent upper respiratory infection. Id. at 2.

A Health Care Plan for the school year of 2011–2012 states that Madison was in the school nurse's clinic twenty-six times during her freshman year. Med. recs. Ex. 31, at 42. During her sophomore year, she had several episodes of unawareness when playing on the soccer team. Id. She had a concussion in September 2010 and discontinued playing at that time. Id.

On February 14, 2012, Madison had an EEG performed due to an episode in January 2012 during which she became lightheaded and dizzy. Med. recs. Ex. 37, at 10. She sat down,

had a glazed and vacant look, and had urinary incontinence. Id. Dr. Mandy O. Harris interpreted the awake and sleep electroencephalogram as normal. Id.

Also on February 14, 2012, Madison saw CPNP Kimberly Minnick. Id. at 7. Madison had been doing well and had gone approximately fifteen months without any episodes. Id. In the last few months, she had started to bleed more heavily during menstruation and had two menstrual cycles in January, both of which were extremely heavy. Id. One week after her last menstrual cycle, she was at school and in weightlifting class. Id. She was spotting for someone else who was lifting weights when Madison's face looked blank and her eyes glazed over. Id. She sat for approximately ten to fifteen minutes and appeared normal and responsive. Id. When she went to another class, she saw she had urinated on herself. Id. Madison had an episode of pain one week previously. Id. While she was eating breakfast, she grabbed her right lower side near the ovarian area. Id. She had some trouble breathing. Id. Madison noticed that since her urine incontinence, she had an increase in headaches. Id. at 8. They occurred every other day and were mild. Id. NP Minnick thought Madison's episodes might be related to confusional migraines. Id. Madison was in the eleventh grade and earning mostly A's and B's, with a few C's in her honors classes. Id. She has seasonal allergies. Id.

On April 24, 2012, Madison saw Dr. Zimmer. Id. at 4. Madison was weaned off Topamax. Id. Madison's mother felt Madison's memory was a bit better. Id. at 5. Madison has not had any recurrences of episodes. Id. She was doing well in school and planning to participate in sports that summer. Id. She was also working at the baseball field and at a custard stand. Id.

On June 26, 2012, Madison saw NP Minnick. Id. at 1. Madison's mother felt Madison continued to have memory and fatigue issues. Id. Madison's mother said there were many times that Madison would just stare. Id. She seemed to respond when someone called her name. Id. This happened almost daily. Id. Approximately one week previously, Madison developed hives mainly on her legs. Id. They were gone in a day and she went to work out for soccer. Id. She was lifting weights and had been lifting them for an hour and one-half when she dropped a bar weighing ninety pounds on her chest. Id. The coach telephoned Madison's mother to say Madison was having an episode. Id. Madison said she felt as if she were stunned or dazed but did not have loss of memory. Id. The coach asked a parent to come and get her, but Madison left with a friend before a parent arrived because she felt fine. Id. at 1–2. Four days after this episode, she developed a headache, which she continued to have over the three to four days prior to her visit. Id. at 2. She complained of temperature instability. Id. Madison finished the eleventh grade with all A's and a few B's. Id. She seemed to have trouble completing tasks. Id. Her goal was to be a personal trainer. Id. Madison had some trouble sleeping due to her temperature regulation problems. Id. Her appetite had decreased lately. Id. She had been more irritable in the last two or three weeks. Id. Madison's mother said Madison was not as excited about soccer or working out as she used to be. Id. Madison mentioned she had a new group of friends. Id. She said she did not feel depressed. Id. Madison was not on any medications. Id. Her blood pressure was 139/77. Id. She was very congested. Id. She had mild periorbital

swelling, most likely due to allergies. Id. Madison had mild pain upon palpation of her frontal sinus area. Id. NP Minnick wrote Madison might have a possible sinus infection. Id. Dr. Zimmer met briefly with Madison's family. Id. Dr. Zimmer said she would try to contact Dr. David Dunn to see if he felt Madison met the criteria for attention deficit disorder. Id. at 3. Depression was also in the differential diagnoses, although it was unclear. Id.

TESTIMONY

The first part of the hearing on April 24, 2012 began with Special Master Zane's summary of the issue in the case: whether or not Gardasil caused Madison's syncope and migraines, an issue to which the parties agreed. Tr. at 6.

Dr. Svetlana Blitshteyn, a neurologist, testified first for petitioner. Tr. at 7–8. She has a subspecialty in autonomic dysfunction. Id. at 9. Madison's first syncope was after her second Gardasil vaccination on September 10, 2007. Three weeks after her third Gardasil on December 31, 2007, Madison experienced dizziness and was unaware of her surroundings. Id. at 12. Doctors considered whether Madison had a seizure disorder but the results of an EEG ruled that out. Id. at 13. Dr. Pappas, a neurologist at Riley Hospital, diagnosed Madison with neurocardiogenic syncope. Id. This means a fainting episode, which, if it becomes chronic, suggests a disorder of the autonomic nervous system. Id.

Dr. Blitshteyn testified that the autonomic nervous system originates from the brainstem and spinal cord through the peripheral nervous system and the nerve endings in that system. Id. at 13–14. It affects almost every organ of the human body. Id. at 14. If the autonomic nervous system malfunctions, people experience a drop in blood pressure and, if they are upright, a loss of profusion to the brain resulting in fainting. Id. The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems. Id. The sympathetic nervous system is the "fight or flight" system and increases heart rate and blood pressure, diverting blood from the major organs to the muscles to prepare someone to flee. The parasympathetic nervous system is more calming. It reduces heart rate and blood pressure, and promotes digestion. Id. The balance between these two nervous systems is very important. Id. There are disorders of both nervous systems, which result in autonomic dysfunction. Id. at 14–15. Neurocardiogenic syncope is one type of autonomic disorder and is quite common. Id. at 15. A second type is postural tachycardia syndrome, a close relative to neurocardiogenic syncope, except that patients do not experience a drop in blood pressure in assuming an upright position, but instead have an inappropriate increase in heart rate. Id. Neurocardiogenic syncope and POTS are on a spectrum, and the same treatment applies to both. Id.

Dr. Blitshteyn testified that after Madison received her third Gardasil, her symptoms got worse. Id. at 16. Between January 2008 and May 2008, her dizziness and altered awareness episodes occurred six to seven times a day and lasted from five to forty minutes. Id. She had dizziness, confusion, altered awareness, disorientation, and partial memory lapses. Id. After May 2008, Madison had spontaneous remission, which lasted for about a year. Id. When

Madison's symptoms recurred, she also developed headaches concurrent with the dizziness, vertigo, and diminished concentration. Tr. at 17. The episodes occurred two to three times a day, lasting about twenty minutes. Id. The possibility of seizures was again refuted. Id. Madison improved on Topamax, which is used for migraine prevention, although she continued to experience episodic dizziness while playing sports. Id.

Madison eventually received a diagnosis of migraine headaches. Id. at 18. Looking back on all her symptoms, Dr. Blitshteyn opined that the headaches were most likely the basilar type of migraine headache. Id. Any migraine is an aberration of the autonomic nervous system. Id.

Dr. Blitshteyn testified that a variety of causes for autonomic dysfunction exists: cold viruses, surgery, pregnancy, and vaccinations. Id. at 19. The most likely mechanism for a vaccine-caused autonomic dysfunction is T-cell response. Id. at 20. Another possible mechanism is cross-reacting antibodies against components of the autonomic ganglia or neurons, which encompasses molecular mimicry. Id. A third mechanism is direct action of the human papillomavirus particles in the vaccine affecting the autonomic nervous system's peripheral ganglia. Id.

Guillain-Barré Syndrome ("GBS") also involves dysautonomia. Tr. at 21. Patients with GBS have fluctuating blood pressure, dilated pupils, and autonomic nervous system abnormalities. Id. Dr. Blitshteyn testified that both GBS and neurocardiogenic syncope have the same mechanism. Id.

Dr. Blitshteyn said that Madison's onset of symptoms six days after her second Gardasil, and symptoms after her third Gardasil is an example of rechallenge. Id. She explained rechallenge as symptoms occurring not after the first vaccination, but after the second vaccination and, specifically, the third vaccination as a booster. Id. at 21–22. Because the immune system is presensitized, every time the same antigen is introduced into the body, the body reacts with a more dramatic immune-mediated response. Id. at 22. In Dr. Blitshteyn's medical practice, she has other patients who have experienced autonomic dysfunction after Gardasil vaccination. Id.

Dr. Blitshteyn said that the onset interval of six days after the second Gardasil vaccination was appropriate for an immune-mediated reaction. Id. at 23. She thinks any interval from days to eight weeks would be an appropriate interval to denote an immune-mediated reaction to the vaccine. Id. Thus, Dr. Blitshteyn testified that petitioner's symptoms three weeks after her third Gardasil was also an appropriate interval for an immune-mediated reaction. Id.

Dr. Blitshteyn stated petitioner has neurocardiogenic syncope and basilar migraines. Tr. at 24. Both of these conditions have roots in the autonomic nervous system and co-exist in patients with autonomic disorders. Id. She does not think petitioner had a primary headache disorder before Gardasil vaccination. Id. at 25. Dr. Blitshteyn stated most of petitioner's pre-existing headaches were secondary to either a concussion or a sinus problem. Id.

Dr. Blitshteyn's opinion is that the second and third Gardasil vaccinations caused petitioner's autonomic disorder, manifesting as recurrent neurocardiogenic syncope and basilar migraines. Id. The most likely mechanism is immune-mediated and molecular mimicry. Id. at 26.

Twenty-five percent of Dr. Blitshteyn's medical practice involves adolescent patients. Id. at 28. These patients all have either autonomic disorders or headaches. Id. She has published three articles on the topic of autonomic disorders. Id. at 29. Migraines are not her specific area of publication. Id. at 30. None of petitioner's doctors ordered autonomic nervous system testing for petitioner. Id. at 33. Dr. Blitshteyn's opinion that petitioner has an autonomic disorder is based solely on petitioner's treating doctors' diagnosis that she has neurocardiogenic syncope. Id. at 34. Petitioner does not have a genetic predisposition for an autonomic disorder because her close relatives do not exhibit similar symptoms. Id. at 35. The most common adverse effect described in the medical articles on Gardasil is a simple faint, i.e., syncope, with a reported rate of 8.2 per 100,000 doses. Id. at 36. There is no data on how many vaccinees go on to develop recurrent and repeated syncope after Gardasil vaccination. Id. Dr. Blishteyn said that the categorization of POTS and neurocardiogenic syncope as disorders of the autonomic nervous system is a new field. Id. at 38.

Dr. Blitshteyn testified that neurocardiogenic syncope and vasovagal syncope are the same. Id. at 38. There are other autoimmune diseases described after Gardasil due to an immune-mediated reaction: acute disseminated encephalomyelitis ("ADEM"), lupus, rheumatoid arthritis, and connective tissue disease. Id. at 38. About one in seven patients with POTS has antibodies identified through the ganglia of the autonomic nervous system. Id. These antibodies are called ganglionic acetylcholine receptor antibodies. Id. at 40.

Dr. Blitshteyn stated that petitioner did not have a simple migraine disorder. Id. at 44. She had basilar type migraines, which are complicated and a rare. Id. at 44. Migraines can occur in the absence of autonomic dysfunction, but there is a high prevalence of migraine in autonomic disorders. Id. at 46.

Dr. Blitshteyn defined neurocardiogenic syncope as a temporary loss of cerebral profusion, resulting in a loss of posture and vasodilation causing fainting. Id. at 57. A variant of syncope is not losing consciousness but losing awareness of one's surroundings. Id. at 58. All of petitioner's episodes were syncopal episodes. Id. To determine the cause of neurocardiogenic syncope, a doctor starts with cardiac testing. Id. at 59. Petitioner had a Holter test, a stress test, an echocardiogram, and an EKG. Id. Her cardiac functions were normal. Id. Once a doctor knows the cause of the neurocardiogenic syncope is not cardiac abnormality, the doctor assumes it is neuro-mediated, i.e., the autonomic control of the cardiac function is malfunctioning. Id. Autonomic dysfunction is indicated by fainting as well as orthostatic intolerance, meaning a drop in blood pressure, which makes standing difficult. Id. at 60. Other symptoms are chronic dizziness, fatigue, and migraine headaches. Id. at 61.

In petitioner's case, there was no evidence of a drop in blood pressure. Id. Dr. Blitshteyn said there should have been a drop in blood pressure even though it was not reported at the time of the syncope. Id. She explained that a blood pressure drop is momentary, and once someone is on the floor, his or her blood pressure may be normal. Id. When petitioner had basilar migraines, she did not have a drop in blood pressure either. Id. at 63. Dr. Blitshteyn said this was because petitioner had an increased overshoot of vasoconstriction. Id. Patients with chronic autonomic disorder feel dizzy, but their blood pressure is normal. Id. at 64. Dr. Blitshteyn said that people with normal blood pressure have other symptoms involving repeated syncope and, after the syncope remits, their symptoms evolve to confusion, vertigo, headache, and basilar migraines, but these symptoms are still part of the autonomic disorder. Id. at 65. She said that whenever someone faints repeatedly, has disabling symptoms, and has lack of function in the context of normal cardiac function and tests, that person has an autonomic disorder. Id.

Petitioner had episodes of dizziness and altered awareness up to six to seven times a day every day from January to May 2008. Id. at 73. From May 2008 to September 2009, petitioner became asymptomatic. Id. at 76. In September 2009, when petitioner began playing soccer, she started having vertigo. Id. at 79. Even though petitioner had been symptom-free for sixteen months, Dr. Blitshteyn views the vertigo as part of the same disorder petitioner developed in reaction to the vaccine. Tr. at 82. She stated that the course can wax and wane. Id. at 83. Even without vaccination, one cannot predict the course of an autonomic disorder. Id. at 84. Dr. Blitshteyn said she does not have evidence that human papillomavirus particles themselves attack the autonomic nervous system. Id. at 86, 90. She said that the process that causes immediate fainting after a vaccination is not known. Id. at 91.

Petitioner's reaction occurred six days after her first vaccination, but reoccurred three weeks after her second vaccination. Id. at 92–93. In her case, the reaction period was longer after rechallenge, rather than shorter. Id. Dr. Blitshteyn said cardiologists and those not specializing in autonomic disorders would typically not say that recurrent neurocardiogenic syncope was autonomic. Id. at 101. Autonomic tests on petitioner were not done. Id. at 102. No doctor diagnosed petitioner with autonomic nervous disorder, but her doctors did diagnose her with neurocardiogenic syncope. Id. Dr. Blitshteyn relates all of petitioner's clinical symptoms—her syncopal episodes, complaints of headache and shortness of breath, and inability to participate in sports—to an abnormal autonomic system. Id.

Petitioner's main problem is that she feels faint and dizzy. Id. at 110. Dr. Blitshteyn said that neurocardiogenic syncope constitutes one-fourth of the autonomic nervous system disorders. Id. at 113. Repeated and chronic passing out or orthostatic intolerance is an autonomic nervous system disorder. Id. at 115. Petitioner did not have any headaches from May 2008 to the fall of 2009. Id. at 133–34. Dr. Blitshteyn does not know what triggered the recurrence of petitioner's symptoms after her May 2008 remission, nor does she believe that anything triggered the recurrence of petitioner's symptoms. Id. at 119. Dr. Blitshteyn believes petitioner spontaneously developed her symptom conflict. Id. No one knows why petitioner had remission. Id. at 139. In her practice, Dr. Blitshteyn sees young teens who cannot go to school

for a year, and then they suddenly get better. Id. at 120. Then they go to college and their symptoms return. Id. There is no way to predict if petitioner will be completely normal in a year, will have a relapsing-remitting course, or will have a chronic course. Id.

Dr. John T. MacDonald, a pediatric neurologist, testified for respondent. Id. at 146. He defined basilar artery migraine as complex migraine syndrome. Id. at 150. Migraine is a paroxysmal disorder with epilepsy, syncope, and headache as primary symptoms. Id. Because of changes in blood flow to the brain and chemical changes to the brain, someone can have a variety of neurological symptoms, some of which relate to the brainstem, that affects a person's ability to stay awake and to control the autonomic nervous system and vestibular inputs from the inner ear. Id. at 150–51. Aura can come before headache, with visual disturbance or lightheadedness, fainting, and loss of consciousness. Id. at 151.

Basilar artery migraine involves a variety of syncopal or presyncopal feelings. Id. at 151. Syncope means passing out or losing consciousness. Id. at 155. Symptoms of basilar artery migraine include ringing in the ears, visual changes, dysarthria (a change in one's voice), vertigo (a spinning sensation), tinnitus (a high-pitched ringing in the ears), hyperacusia (overreaction to normal auditory stimuli), diplopia (double vision), ataxia (difficulty with balance), and bilateral paresthesias (odd feelings in one's body, such as numbness and tingling). Id. at 152–53. The most common migraine symptoms are changes in the visual fields. Id. Some people cannot see parts of their visual field, or they see wavy lines, spots, and distortions. Id. at 153. Presyncope, syncope, or confusional states involve a decreased level of consciousness. Id.

Complicated migraine involves certain parts of the nervous system where blood flow is impaired. Id. If the visual system is involved, the person has visual changes. Id. If the vestibular system is involved, the person may have syncope, near syncope, vertigo, dizziness, and tinnitus. Id. If the brainstem is involved, the person may pass out or become ataxic and appear to be drunk. Tr. at 153–54. The cause of migraine is a vascular phenomenon involving chemical and neurotransmitter abnormalities in the arteries feeding the brain. Tr. at 154. There are also various triggers and genetic factors. Id.

Triggers for migraines are endless. Id. These triggers provoke the biochemical or vascular change in the brain. Id. Some people are very sensitive to light, certain foods, stress, and lack of sleep. Id. Migraines are quite common and are much more common in children. Tr. at 155. After puberty, girls outnumber boys in having migraines. Id.

Syncope is one of the paroxysmal disorders. Id. In children, it is frequently a differential diagnosis with epilepsy since children who hold their breath can pass out five or ten times an hour. Id. Reflex syncope is the same as vasovagal syncope. Tr. at 157. There can be many triggers, including emotional issues. Id.

When someone, such as Madison, passes out during exercise, a physician would want to make sure that the person does not have a primary structural or electrical heart problem. Tr. at

158. For this reason, Madison was sent to a cardiologist, who found she did not have a structural defect. Id. Exertional or peri-exertional syncope is the same as vasovagal syncope unless there is a structural or functional heart defect. Id. Vasovagal syncope has been associated with syringes when someone sees a needle. Tr. at 159. Most of the syncope occurs in the doctor's office or immediately following the procedure. Id. Migraines can cause syncope. Id.

Dr. MacDonald stated that migraines can change a person's autonomic nervous system, leading to syncope. Tr. at 161. Dr. MacDonald does not agree with Dr. Blitshteyn that a disorder of the autonomic nervous system can cause a migraine or a headache. Id. He thinks Dr. Blitshteyn has the causal order reversed, i.e., it is the migraine that causes the change in the autonomic nervous system leading to syncope, and not the reverse with the autonomic nervous system change leading to migraine and syncope. Id. Dr. MacDonald would not diagnose Madison with a primary autonomic nervous system disorder. Id.

Dr. MacDonald said he did not know of any medical literature discussing whether Gardasil vaccine causes primary autonomic nervous system disorders. Id. at 162. He thought the case report of POTS that Dr. Blitshteyn wrote was vague as to onset and the occurrence of other illnesses that could equally have caused POTS. Id. at 162–63.

Dr. MacDonald described Madison's case and stated she had headaches before Gardasil vaccination, but he does not know if they were due to concussion or sinusitis. Id. at 163. Children with migraine usually have symptoms years before that exclude headache. Id. at 163–64. He has seen children who were cyclic vomiters, vertiginous, or fainters later develop migraine. Id. at 164. Sinus headaches in young children are unusual, and even though doctors diagnose them as sinus headaches, they are probably low-grade migraines. Id. A child with a migraine tendency is more likely to develop a post-concussive headache. Id.

Dr. MacDonald believes that Madison had a tendency to migraine earlier in her life, which mild sinus disease or headache may have triggered. Id. Migraine is an inherited tendency. Id. Madison had an episode during track, but it is unclear to Dr. MacDonald if she actually lost consciousness or was just confused. Id. It is also unclear to Dr. MacDonald if Madison had syncope with that episode. Id. at 165. Confusion migraine is another subset of migraine, in which children get very confused and disoriented but can still talk. Id. at 164–65.

Madison continued to have episodes that were either syncope or presyncope, dizziness, and some vertigo. Id. Even with more spells in early 2008, Madison was still attending school and getting good grades. Id. In between episodes, Madison appeared normal. Id. Eventually, the episodes improved, went away for a while, and came back. Id. The headaches became a bigger issue. Id. Dr. MacDonald stated that when the brainstem or vestibular system is affected, symptoms of dizziness, vertigo, syncope, or presyncope appear. Id. These symptoms can predate headaches by years. Id. A diagnosis of migraine is important because drugs like Topiramate [Topamax] can be helpful. Id. Topiramate is an anticonvulsant, but it also prevents migraines. Id. at 166–67. Madison did very well on Topiramate. Id.

Dr. MacDonald would diagnose Madison as having confusional vestibular migraine presenting early with vasovagal symptoms (presyncope, dizziness, vertigo) and later headaches. Id. at 166. Variability in the frequency of episodes is typical. Id. Doctors look for triggers. Id. The fact that Madison did well on Topiramate tells Dr. MacDonald that her complicated migraine pattern explains the vast majority of her symptoms because he would not expect Topiramate to have positively affected Madison otherwise. Id. at 167–68. In Dr. MacDonald's opinion, the fact that Madison was not helped by Keppra, which does not prevent migraine, confirms her migraine diagnosis. Id. at 168.

Dr. MacDonald did not see any dramatic change in Madison after her third Gardasil vaccination. Id. In 2009, all of Madison's spells were in school. Id. at 169. Dr. MacDonald thinks that the stress of trying to get good grades brought out her spells. Id. The number of spells does not indicate severity to Dr. MacDonald. Id. Madison got better, and she has had a few episodes since. Id.

Madison's doctors did not consider her vaccination to have caused her spells and did not order a large group of immunologic tests. Id. at 170. Dr. MacDonald said there is no evidence of a more global involvement of Madison's central nervous system than her spells. Id. He testified it would be very unusual for the autonomic nervous system to be an isolated target. Id. The fact that Madison recovered between spells shows she was not encephalopathic. Id. She did not have fever or other neurologic symptoms. Id. at 170–71. All we have are the spells and normalcy in between. Id. at 171. Dr. MacDonald does not believe that Gardasil played any role in causing Madison's condition. Id. While there is temporal association between Gardasil and her condition, the migraine explanation is obvious and explains almost all of it. Id. Madison had some vasovagal spells that went away, and she was back to normal. Id. Dr. MacDonald viewed the theory of an isolated but pernicious immunologic attack on just the autonomic nervous system as "a stretch of logic that I just can't make." Id.

Dr. MacDonald does not think Madison's resumption of spells after her third Gardasil vaccination indicates rechallenge. Id. at 191. He regards the nature of her problem as periods of remission and periods of more dramatic symptoms for which there can be all kinds of triggers. Id. The beginning of the school year coincided with her worsening spells in the autumn. Id. All her episodes occurred in school. Id. at 191–92. He regards Madison's onset of spells six days after her second Gardasil vaccination and her resumption of spells two or three weeks after her third Gardasil vaccination as "a purely temporal association," particularly in light of her having a flare up of symptoms in 2009 when she did not have a Gardasil vaccination. Id. at 197.

Dr. MacDonald said, in vasovagal syncope, the autonomic nervous system briefly functions abnormally but is normal in between spells. Id. at 205. In his mind, this brief malfunction of the autonomic nervous system does not constitute an autonomic nervous system disease. Id. He is impressed that Madison always goes back to normal between her spells. Id. at 207. All her examinations and testing are normal. Id. If Madison had a permanent alteration in

her autonomic nervous system, Dr. MacDonald would expect her to have either chronic problems that do not improve or a progressive disease. Id. Dr. MacDonald thinks Madison's course is consistent with migraine and she probably has the vasovagal issues in addition to migraine. Id. He does not think Madison has an autonomic nervous system disorder, id. at 208, but rather thinks that the primary actor is the migraine syndrome. Id. at 214. The migraine syndrome causes abnormalities of the autonomic nervous system. Id. Migraine can affect the vestibular system, causing vertigo. Id.

In pediatric neurology, many younger patients have symptoms of migraine without headache for years. Id. at 215. They eventually develop migraine years later. Id. The way migraine produces the symptoms is by affecting the autonomic nervous system. Id. at 217. It does not involve a primary disorder of the autonomic nervous system. Id. at 217–18.

Madison's migraines did not begin until two years after she developed a syncopal episode. Id. at 222. Before Madison received Gardasil vaccine, she fell on her head, and while in the emergency room after falling on her head April 30, 2007, she remarked she had no recall of events. Id. at 223. Dr. MacDonald said this was a common problem. Id. He said this could have been a syncopal spell. Id. at 224. Madison was diagnosed with concussion. Id. at 225.

In answer to Special Master Zane's questions, Dr. MacDonald said that the interval of six days between Madison's second Gardasil vaccination and her syncope was an appropriate temporal relationship. Id. at 226. He also agreed that two weeks between the third Gardasil and syncope was an appropriate temporal relationship. Id. at 228. He agreed that molecular mimicry was a plausible medical theory to connect Gardasil and neurocardiogenic syncope:

> THE COURT: Okay. And then also I wanted to ask you about the medical theories because in terms of [sic] Dr. Blitshteyn had set forth three theories, and she set forth – where is my paper? She set forth a theory of molecular mimicry, a theory of an immune-mediated reaction triggered by the vaccine and then a third theory of direct action of HPV particles on the autonomic nervous system, okay?
> THE WITNESS: Right.
> THE COURT: Okay. Now, let's start with the No. 1. Do you agree that that's a plausible medical theory or not?
> THE WITNESS: Yes.

Id.

Dr. MacDonald said he was "not so hot for" Dr. Blitshteyn's second theory: immune-mediated reaction triggered by Gardasil. Id. He said there is a lot less science to support that theory, unlike molecular mimicry: "The molecular mimicry I have no trouble with." Id. at 229. He viewed Dr. Blitshteyn's third theory—direct action of human papillomavirus particles on the

autonomic nervous system—as "really speculating." Id. He said he would "rather stay with No. 1." Id.

Dr. MacDonald admitted in response to Special Master Zane's question that vaccines can trigger migraines. Id. at 242, 247. Migraine is an episodic disorder, and variability is just part of the process. Id. at 243. A person with migraines inherits the tendency, but there is no indication in the records than anyone in Madison's family had a history of migraines. Id. at 245–46. The autonomic nervous system does not cause headache unless someone passes out. Id. He would not be surprised if a vaccine could trigger migraine. Id. at 247. He does not think Madison had any psychiatric problems. Id. at 150. We do not know what the stressors are. Id. at 251. If someone has a predisposition to migraine, at some point it will manifest itself. Id. at 256. Migraine attacks the autonomic nervous system but does not destroy or injure it. Id. at 259.

The hearing ended for the day and resumed on December 13, 2012, almost eight months after the first part of the hearing.[10] Dr. Blitshteyn, testifying first, stated that when Madison had her first episodes after her second Gardasil, she did not have migraine headache. Dec. Tr. at 15. She had dizziness, lightheadedness, loss of consciousness, presyncope, orthostatic intolerance, and exercise intolerance. Id. She had neurocardiogenic syncope. Id. Madison was prescribed Florinef, which treats autonomic dysfunction. Id. at 16. Florinef is never prescribed for headache. Id. Neurocardiogenic syncope is a close variant of POTS. Id. at 17. The Mayo Clinic did a study and found a subset of 10–14 percent of patients with POTS had antibodies to the acetylcholine ganglionic receptor. Id. That receptor is located between the cluster of neurons in the peripheral nervous system and transmits messages from the brain and spinal cord to the extremities. Id. Dr. Blitshteyn considers proof of an autoimmune etiology is the autoimmune etiology of POTS. Id.

Dr. Blitshteyn said that many patients with POTS have an autoimmune etiology because they have their onset after a virus or infection. Id. at 18. In addition, patients with autonomic neuropathy can have symptoms after immunization, suggesting an autoimmune etiology. Id. Both neurocardiogenic syncope and POTS are disorders of orthostatic intolerance and are disorders of the autonomic nervous system. Id. at 19.

Dr. Blitshteyn said Madison had a period of time when her symptoms regressed, which is common for patients with POTS and with neurocardiogenic syncope. Id. at 22. Neurocardiogenic syncope is a disorder of the autonomic nervous system. Id. at 35–36. A regression in symptoms may also correlate with a decline in antibodies. Id. at 22. Lower titers of ganglionic acetylcholine receptor antibody are often found in milder forms of autonomic neuropathy, such as POTS and neurocardiogenic syncope. Id. at 24. The waxing and waning of symptoms correlate to the antibody levels. Id. at 25. Antibody levels were not drawn for

[10] The pagination of the transcript starts with page 1. For clarity, references to the transcript will be cited as "Dec. Tr. p. []."

Madison, but one can make a diagnosis of neurocardiogenic syncope without doing a test for these antibodies. Id. at 27.

Madison was diagnosed with neurocardiogenic syncope but was not diagnosed with POTS. Id. at 36. She was diagnosed with a limited form of autonomic neuropathy. Id. at 37. Dr. Blitshteyn considers Madison's migraine, which developed later than her symptoms of neurocardiogenic syncope, as a co-morbid disorder. Id. at 49. Dr. Blitshteyn considers Madison's episodes after her third Gardasil a rechallenge, even though the onset was weeks and not quicker than her onset of symptoms after the second Gardasil. Id. at 53–54. She disagrees that migraine can cause syncope. Id. at 54. In patients with migraine, there seems to be a higher incidence of syncope, meaning migraine and syncope are co-morbid conditions. Id. More than 20 percent of patients with POTS and neurocardiogenic syncope also have migraine. Id. at 56. Madison had protracted dizziness, lightheadedness, and syncope for more than a year before she had migraines. Id. Neurocardiogenic syncope is a drop in blood pressure when someone stands up. Id. at 63. In order to have neurocardiogenic syncope, someone must have a drop in blood pressure. Id. The drop in blood pressure is so severe, there is no blood going to the brain, resulting in syncope. Id. at 64. POTS patients do not have a drop in blood pressure. Id. They have increased tachycardia, a different mechanism, resulting in orthostatic intolerance. Id.

Doctors should suspect autoimmune pathogenesis when a viral illness or an immunization is an antecedent to the onset of an autonomic disorder. Id. at 65. Viral illnesses and immunizations are known to be triggers for certain diseases. Id. at 66. Some autonomic neuropathies do not have an autoimmune pathogenesis, and doctors call them idiopathic. Id. When a disorder is hereditary, it is not autoimmune. Dec. Tr. at 67. Migraines have a hereditary component. Id. Madison has recurrent orthostatic intolerance, which to Dr. Blitshteyn means she has a limited form of POTS. Id. at 68.

Dr. MacDonald explained his prior answer to former Special Master Zane's question that petitioner's theory of molecular mimicry was a plausible theory of causation by stating he meant he accepts it as a plausible theory, but not as applied in this case:

> Q [by respondent's counsel]: In response to a question by the Special Master at the earlier hearing in this case you said that molecular mimicry was a plausible theory. To be clear, are you saying that molecular mimicry is a plausible theory in the context of this case?
> A. No. I accept that as a theory that's plausible, but I don't think we can apply it in this case.

Id. at 73.

Dr. MacDonald said he distinguished between trigger and cause. Id. He does not think Gardasil caused Madison's neurocardiogenic syncope because a combination of migraine and vasovagal syncope explains what happened to her. Id. He thinks there was no rechallenge because Madison's onset of six days after the second Gardasil was too long if the first Gardasil had sensitized her. Id. at 74. He does not think Madison's symptoms after her third Gardasil were worse than her symptoms after the second Gardasil and he does not see any rechallenge there either. Id. He explained that a complicated migraine is more than just headache. Id. at 75. Madison had a complicated migraine, which explains most of her symptoms. Id. Dr. MacDonald again agreed that a six-day onset after the second Gardasil was appropriate for an immune-mediated reaction, and the temporal interval after the third Gardasil was also appropriate although he would have liked to have seen a shorter interval such as a day and more dramatic symptoms. Id. at 78, 80. In his opinion, Madison had migraine headaches, some vertigo, and dizziness before she received Gardasil. Dec. Tr. at 83. He thinks that Madison's sinusitis was coincidental to and not causal of her headaches pre-vaccination, and he is skeptical about the diagnosis of concussion ("I think that's what they thought") when she fell on her head pre-vaccination. Id. at 83, 84.

Dr. MacDonald did not consider the resumption of Madison's near syncope one week after her third Gardasil to be a worsening of her condition because her episodes were brief. Id. at 100. She had four to five episodes a day and was disoriented and confused. Id. She could not feel her extremities moving during these episodes. Id. Florinef is not prescribed for migraines. Id. at 102. Dr. MacDonald thinks migraine and autonomic nervous system disorder are co-morbidities in that migraine causes the autonomic dysfunction, which then causes syncope. Id. at 118.

Dr. MacDonald said that there is no evidence that Madison's immune system was altered and, therefore, molecular mimicry is inapplicable here, although molecular mimicry is a plausible theory of how autoimmunity occurs. Id. at 119, 120. Dr. MacDonald would not apply the studies on POTS that petitioner filed to Madison because she was not diagnosed with POTS. Id. at 141.

Dr. Blitshteyn responded to Dr. MacDonald's testimony concerning Madison's condition after the third Gardasil. Id. at 154. She said Madison's symptoms after her third Gardasil were significantly exacerbated from January to May 2008 because she had episodes of dizziness and altered awareness up to six or seven times daily, lasting five to forty minutes. Id. Her symptoms also included pallor, diaphoresis, altered awareness of her surroundings, confusion over people's names, disorientation, and partial memory lapses. Id.

Other Filed Material

On June 23, 2011, petitioner filed the expert report of Dr. Blitshteyn as Exhibit 27, together with 10 attachments (Tabs A–K) and her curriculum vitae (Exhibit 28). Dr. Blitshteyn reviews Madison's medical history and concludes that Gardasil caused Madison both

neurocardiogenic syncope and basilar migraine. Ex. 27, at 3. Madison's treating neurologist, Dr. Jennifer Zimmer, diagnosed Madison in September 2009 with basilar migraine after one and one-half years of remission from neurocardiogenic syncope. Id. Dr. Blitshteyn's basis for her opinion is: (1) the close temporality of six days between onset of Madison's neurocardiogenic syncope after her second Gardasil; (2) her worsening symptoms three weeks after her third Gardasil; and (3) the common pathophysiologic mechanisms that neurocardiogenic syncope and basilar migraine share, i.e., a disturbance in the function of the autonomic nervous system. Id.

Dr. Blitshteyn notes that "chronic and recurrent syncope as part of an autonomic disorder after vaccination with Gardasil has not been well-described in literature and has not yet received the attention of the research community that it deserves." Id. at 4. She identifies POTS as a disorder of the autonomic nervous system closely related to neurocardiogenic syncope, and has written a case report on a young woman who developed POTS two weeks after receiving Gardasil (Ex. 27, Tab E). Id. Dr. Blitshteyn says that, in her clinical practice, consisting of patients with autonomic and other neurologic conditions, she has several other young women who developed neurocardiogenic syncope or POTS within weeks of receiving Gardasil. Id. Her impression is that "Gardasil vaccine may be a potential precipitating factor in the development of these autonomic disorders in a subset of young women." Id.

Dr. Blitshteyn propounds three possible mechanisms for what she terms "post-vaccination autonomic disorders," such as POTS or neurocardiogenic syncope: (1) immune-mediated reaction to vaccine; (2) formation of cross-reacting antibodies against components of the autonomic ganglia or neurons as part of the autoimmune process, i.e., molecular mimicry; and (3) direct action of human papillomavirus-like particles from Gardasil on the autonomic nervous system. Id. at 4–5.

Attached to Dr. Blitshteyn's expert report is her Letter to the Editor published in the European Journal of Neurology. Ex. 27, Tab E (S. Blitshtyen, Postural tachycardia syndrome after vaccination with Gardasil, 17 Eur. J. Neurology e52 (2010)). Her letter deals with a 20-year-old woman who had the onset of POTS two weeks after receiving her first Gardasil. Ex. 27, Tab E. She had dizziness, exercise intolerance, fatigue, nausea, and a loss of appetite. Id. A tilt table test confirmed she had POTS. Id. The patient tested negative for ganglionic acetylcholine receptor antibody. Id. Dr. Blitshteyn writes that an autoimmune etiology for POTS has been implicated in about 14 percent of patients with POTS after detection of ganglionic acetylcholine receptor antibody. Id. Reflecting that autonomic disorders can coexist with autoimmune diseases (although none were identified in this case), she also writes, "the temporal relationship between vaccination and illness onset suggests a possible association between *de novo* POTS and vaccination with Gardasil." Id. She states that POTS is viewed as an attenuated form of the autoimmune autonomic ganglionopathy, which can be seronegative for ganglionic acetylcholine receptor antibody, as in this case. Id. She posits that since cross-reacting antibodies are found in various post-vaccination illnesses, such as GBS and transverse myelitis, "it is conceivable that a cross-reacting, yet unidentified, antibody other than to ganglionic acetylcholine receptor may underlie the pathogenesis of POTS in the setting of an antecedent vaccination." Id. Dr.

Blitshteyn admits that POTS has not been identified as an adverse event in a postlicensure safety surveillance of Gardasil, but states "it is probable that some patients who develop POTS after immunization with Gardasil or other vaccines are simply undiagnosed or misdiagnosed, which leads to under-reporting and a paucity of data on the incidence of POTS after vaccination in literature." Id. She says her letter is the first case report describing POTS after Gardasil and alerts physicians to be aware of a possible association between the two. Id.

Dr. Blitshteyn expands on this Letter to the Editor in another article petitioner filed on October 24, 2013. Ex. 47 (S. Blitshteyn, Postural tachycardia syndrome following human papillomavirus vaccination, 21 Eur. J. Neurology 135 (2014)).[11] In this article, Dr. Blitshteyn uses the patient she described previously in her Letter to the Editor (Ex. 27, Tab E) as the first of six patients who developed POTS six days to two months after receiving Gardasil. Ex. 47, at 1, 2, 4. Dr. Blitshteyn states that POTS is a heterogeneous disorder. Id. at 4. She says that POTS may arise from various mechanisms and etiologies, but recently there is evidence that POTS may be an autoimmune disorder. Id. Based on the finding of several types of antibodies in patients with POTS, Dr. Blitshteyn writes she considers POTS "an attenuated form of autoimmune autonomic neuropathy in a subset of patients." Id. The antibodies she describes are to ganglionic N-type acetylcholine receptors, various cardiac proteins, and ß1/2 adrenergic and M2/3 muscarine receptors. Id. She writes possible pathogenesis of POTS after Gardasil may include molecular mimicry, in which human papillomavirus vaccine epitopes may induce formation of cross-reacting antibodies against potential targets of the autonomic ganglia, neurons, cardiac proteins or ß1/2 adrenergic and M2/3 muscarine receptors. Id. She also states that bystander lymphocyte activation and a broad spectrum of cytokine responses that human papillomavirus vaccine elicits may also be involved. Id. Dr. Blitshteyn relates the subjects' onset of POTS to the onset periods of GBS and ADEM after vaccination and says they are consistent with these well-known post-vaccination syndromes. Id.

Also attached to Dr. Blitshteyn's expert report is an article published in the Journal of Cardiovascular Electrophysiology. Ex. 27, Tab H (B.P. Grubb et al., Postural Tachycardia Syndrome: a concise guide to diagnosis and management, 17 J. Cardiovascular Electrophysiology 108 (2007)). The authors state that POTS is a subgroup of neurocardiogenic syncope. Ex. 27, Tab H, at 108. They state that POTS is a similar, but distinct, disorder from neurocardiogenic syncope and is manifested by postural tachycardia and exercise intolerance. Id. They also state that POTS encompasses a heterogeneous group of disorders that share similar clinical characteristics. Id. The authors categorize POTS as either primary or secondary. Id. The primary POTS group is unrelated to any other disease, whereas secondary POTS is related to a known disease. Id. The most common form of primary POTS is called "partial dysautonomic" because patients seem to have "a mild type of peripheral autonomic neuropathy characterized by an inability of the peripheral vasculature to constrict in the face of orthostatic stress." Id. Many patients report abrupt onset after febrile illness, pregnancy, immunizations, sepsis, surgery, or trauma. Id. The authors state, "It is currently felt that this form of POTS has an immune-

[11] References will be to the page numbers of the electronic version, filed as Exhibit 47.

mediated pathogenesis. Studies have demonstrated serum autoantibodies to alpha$_3$ acetylcholine receptors of the peripheral autonomic ganglia in patients with postviral autonomic neuropathy." Id.

The authors write there is a second type of partial dysautonomic POTS that affects adolescents, which they term "developmental" Id. Onset is usually around 14 years of age, often after a growth spurt. Id. Symptoms usually worsen and reach their peak around age 16. Id. Symptoms of orthostatic intolerance and often severe headaches may be so intense that the patient is functionally disabled. Id. Symptoms then slowly ameliorate so that by young adulthood, 80 percent of patients are asymptomatic. Id. The etiology is unclear but may reflect autonomic imbalance in rapidly growing adolescents. Id. at 109.

The authors identify a second, less common, form of primary POTS that appears to be genetically caused, which they call "hyperadrenergic". Id. The onset is gradual with symptoms including significant tremor, anxiety, and cold sweaty extremities. Id.

Turning to secondary POTS, the authors refer to conditions causing peripheral autonomic deinnervation but sparing cardiac innervation, such as: diabetes mellitus, amyloidosis, sarcoidosis, alcoholism, lupus, Sjogren's Syndrome, heavy metal intoxication, and effects of chemotherapy. Id. Secondary POTS can also be caused by an inherited disease called joint hypermobility syndrome, which is a connective tissue disorder. Id. POTS may also present as a more severe autonomic nervous system disorder such as pure autonomic failure or multiple system atrophy. Id. Additionally, POTS may present as a paraneoplastic syndrome associated with adenocarcinomas of the lung, breast, ovary, and pancreas. Id. These tumors produce autoantibodies against acetylcholine receptors in the autonomic ganglia, similar to what occurs in post-viral syndromes. Id. at 109-10.

The authors note that about half of patients suffering from post-viral POTS will make a good recovery over two to five years. Id. at 112. In general, the younger the patient, the better her outcome. Id. About 75 percent of adolescents with "developmental" POTS will recover significantly by their early to mid-twenties. Id.

Also attached to Dr. Blitshteyn's expert report is an article published in the Journal of the American Medical Association. Ex. 27, Tab I (B.A. Slade et al., Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine, 302 J. Am. Med. Ass'n 750 (2009)).[12] The purpose of the article was to summarize reports made to the Vaccine Adverse Event Reporting System (VAERS) from June 1, 2006 to December 31, 2008, after 23 million doses of Gardasil vaccine were administered. Ex. 27, Tab I, at 751. There were 1,896 reports of syncope or syncope vasovagal, 90 percent of which occurred on the same day as vaccination. Id. at 752–53. There were 1,572 reports of dizziness, 75 percent of which occurred on the same day as vaccination. Id. There were 1,164 reports of nausea, 63 percent of which

[12] This is also respondent's Exhibit A1, attached to respondent's expert Dr. MacDonald's report.

occurred on the same day as vaccination. Id. Half of the events occurring on the same day as vaccination occurred within 15 minutes after vaccination. Id. at 753. The authors note that vasovagal syncope was among the most reported adverse events following Gardasil immunization. Id. at 756.

On December 3, 2012, petitioner filed Exhibits 39–45. Exhibit 39 is another medical article, B.P Grubb, Neurocardiogenic Syncope and Related Disorders of Orthostatic Intolerance, 111 Circulation 2997 (2005). Unlike his article about POTS two years later (Ex. 27, Tab H), in which he called POTS a subgroup of neurocardiogenic syncope, in this article about neurocardiogenic syncope, Grubb has a chart of disorders of the autonomic nervous system associated with orthostatic intolerance, dividing into three the categories of reflex syncope, POTS and autonomic failure. Id. at 2999. Under the reflex syncope category, Grubb puts two subcategories: neurocardiogenic syncope and carotid sinus hypersensitivity. Id. Under the POTS category, Grubb puts primary and secondary POTS with their sub-subcategories. Id. Under the autonomic failure category, he puts two subcategories: acute and chronic with their various sub-subcategories. Id. Grubb states, "The cause of neurocardiogenic syncope is unclear. It can be brought on by pain, emotional distress, or by prolonged standing (especially in very warm environments), yet many episodes occur without any specific provocation." Id. Grubb states current medical belief is that neurocardiogenic syncope is related to prolonged orthostatic stress. Id. He writes, "What distinguishes the reflex syncopes from the other conditions discussed herein is that between episodes of syncope, these patients complain of few (if any) autonomic symptoms." Id. at 3000. "Thus, in this group, the autonomic system appears to function in a relatively normal manner, despite being somewhat 'hypersensitive,' as opposed to other conditions in which the autonomic system appears to 'fail,' functioning at a level inadequate for the body's needs, which results in varying degrees of orthostatic intolerance." Id.

On September 19, 2011, respondent filed the expert report of Dr. MacDonald as Exhibit A. His opinion is that most of Madison's symptoms are related to her underlying migraine, taking the form of a basilar-type or syncopal migraine. Ex. A, at 2. He does not see any objective evidence relating her condition to Gardasil. Id. He mentions that when syncope is due to Gardasil, it occurs within minutes of vaccination. Id. He says that syncope and migraine are common in Madison's age group. Id. Dr. MacDonald states that medical literature describes many cases of syncope having a migrainous etiology. Id. He says that Madison's headaches preceded the receipt of her second Gardasil. Id. The medical records for April 30, 2007 also mention dizziness. Id. This suggests to Dr. MacDonald that Madison's syncopal migraine disorder preceded the onset of her first syncopal episode post-Gardasil. Id. He says that many children with migraine have onset during periods of illness, stress, or minor head injury. Id. Dr. MacDonald opines that the Gardasil vaccinations were most likely coincidental to her syncopal episodes. Id. Usually, Dr. MacDonald's adolescent patients with syncope and headache have good clinical response to Topamax, which is an anti-migraine medication. Id. Criticizing Dr. Blitshteyn's expert report, Dr. MacDonald doubts the third Gardasil aggravated her syncopal episodes because Madison did not have an immediate, marked acute exacerbation as one would expect if there were a pathological connection between Gardasil and Madison's disorder. Id. at

3. He states there is no objective evidence of an immune-mediated reaction in Madison's case after the second Gardasil. Id. Respondent filed Dr. MacDonald's curriculum vitae as Exhibit B.

On September 30, respondent filed Exhibits A1 to A9, the medical literature to which Dr. MacDonald referred in his expert report. The undersigned has already discussed Exhibit A1, which is identical to petitioner's Exhibit 27, Tab I (the Slade article on postlicensure surveillance). Exhibit A2 is an article entitled "Reflex syncope in children and adolescents." W. Wieling et al., Reflex syncope in children and adolescents. 90 Heart 1094 (2004). The authors describe a combination of peripheral arterial and venous vasodilation which relative bradycardia closely follows as the most common physiologic occurrence observed during spontaneous or induced syncopal events in young people. Ex. A2, at 1094. Terms to describe this experience include simple faint, vasovagal, vasodepressor, and neurocardiogenic syncope. Id. Episodes may occur during strenuous exercise. Id. at 1095. Actual loss of consciousness occurs only in a minority of POTS patients. Id. The authors state that basilar migraine can cause syncope. Id. at 1097. Attacks may start with bilateral visual symptoms, vertigo, syncope, and more typical migraine, but the headache may not always be present. Id. "Arterial pressure [in basilar migraine] is typically normal or mildly elevated, but not reduced, supporting local restriction of brain blood flow as the mechanism." Id.

The undersigned has not included a description of all the medical articles both parties filed in this case, but the undersigned has read them.

DISCUSSION

To satisfy her burden of proving causation in fact, petitioner must prove by preponderant evidence: "(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 vaccination and injury." Althen v. Sec'y of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of Health and Human Services, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" the logical sequence being supported by "reputable medical or scientific explanation[,]" i.e., "evidence in the form of scientific studies or expert medical testimony[.]"

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. Id. at 1148.

Petitioner must show not only that but for her human papillomavirus vaccination, she would not have had neurocardiogenic syncope, but also that the vaccine was a substantial factor

in causing her neurocardiogenic syncope. Shyface v. Sec'y of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

The Vaccine Act does not permit the undersigned to rule in favor of petitioner based solely on her allegations unsupported by medical records or credible medical opinion. 42 U.S.C. § 300aa-13(a)(1).

First Prong of Althen

Dr. Blitshteyn's medical theory explaining how Gardasil can cause neurocardiogenic syncope is that it is a variant of POTS, and POTS has an autoimmune pathology. However, the medical literature that petitioner filed belies that theory. First, neurocardiogenic syncope and POTS are not variants. According to the 2007 Grubb article, POTS is a subgroup of neurocardiogenic syncope. Ex. 27, Tab H. Not all neurocardiogenic syncope patients have POTS. Petitioner does not have POTS. An explanation of the pathology of POTS that applies to just a subset of POTS patients is not transferable to neurocardiogenic syncope, which illness Dr. Blitshteyn testified medical researchers have not studied. Moreover, Grubb and his co-authors in the 2007 article depict POTS patients as a heterogeneous group. (Dr. Blitshteyn makes this same statement about POTS in her article about six POTS patients. Ex. 47.) Not all POTS patients have an immune basis for their illness. Therefore, not all POTS patients have an autoimmune pathology to explain their condition.

Dr. Blitshteyn mentions in her Letter to the Editor that only 14 percent of POTS patients have an autoimmune etiology implicated after detection of ganglionic acetylcholine receptor antibody. Ex. 27, Tab E. The young patient who is the subject of Dr. Blitshteyn's Letter to the Editor did not have antibodies to ganglionic acetylcholine receptors, although she has POTS. Therefore, Dr. Blitshteyn could not rely on the patient's having ganglionic acetylcholine receptor antibodies as the basis for her opinion that her patient's POTS was due to the Gardasil vaccination she received two weeks before onset of her POTS. Dr. Blitshteyn relies instead on an unknown antibody to speculate that Gardasil caused this young woman's POTS: "[I]t is conceivable that a cross-reacting, yet unidentified, antibody other than to ganglionic acetylcholine receptor may underlie the pathogenesis of POTS in the setting of an antecedent vaccination." Ex. 27, Tab E. This is a conclusion in search of a basis.

Dr. Blitshteyn expands her analysis of POTS as an autoimmune disease in her article filed as Exhibit 47, in which she says that POTS may arise from various mechanisms and etiologies, but refers to recent evidence that POTS may be an autoimmune disorder. Based on the finding of several types of antibodies in patients with POTS, Dr. Blitshteyn writes she considers POTS an attenuated form of autoimmune autonomic neuropathy in a subset of patients. Note that a subset of POTS patients does not include all POTS patients and, furthermore, petitioner herein does not have POTS. She has neurocardiogenic syncope. In the article (exhibit 27), Dr. Blitshteyn identifies the antibodies that have been described in that POTS subset which she considers an attenuated form of autoimmune autonomic neuropathy: the receptors are to

ganglionic N-type acetylcholine receptors, various cardiac proteins, and ß1/2 adrenergic and M2/3 muscarine receptors. Petitioner has not filed proof that she has antibodies to ganglionic N-type acetycholine receptors, various cardiac proteins, or ß1/2 adrenergic and M2/3 muscarine receptors. The autoimmune theory that may apply to this POTS subset does not apply to petitioner.

Dr. Blitshteyn writes in her later article that a possible pathogenesis of POTS after Gardasil may include molecular mimicry, in which human papillomavirus vaccine epitopes may induce formation of cross-reacting antibodies. Ex. 47. A spectrum of cytokine responses elicited by human papillomavirus vaccine may also be involved. Dr. Blitshteyn says potential targets are the autonomic ganglia, neurons, cardiac proteins, or ß1/2 adrenergic and M2/3 muscarine receptors. She also states that bystander lymphocyte activation may be involved. She further relates the subjects' onset of POTS to the onset timeframes of GBS and ADEM after vaccination, and she says they are consistent with these well-known post-vaccination syndromes. Dr. Blitshteyn's reasoning in her article is strikingly similar to her testimony in this case in 2012, a year before publication. Yet, her possible theories to explain how Gardasil causes neurocardiogenic syncope are insubstantial. These are all suppositions based on no data—not just insufficient data, but no data at all. Not only has petitioner not been examined for any of these suspect antibodies, but also no patient with neurocardiogenic syncope has been examined for these suspect antibodies. Dr. Blitshteyn's attempt to transplant theories of autoimmunity, bystander activation, or cytokine responses from well-known demyelinating neurological diseases, such as GBS and ADEM, onto neurocardiogenic syncope for which there is no pathologic explanation at present, is unavailing.

Dr. Blitshteyn relies principally on timing for her opinion of causation, but timing, as numerous decisions hold, is legally insufficient to prove causation in fact. See, e.g., Grant, 956 F.2d at 1148. The timing she chooses as appropriate to connote an autoimmune reaction, six days after the second Gardasil and three weeks after the third Gardasil, is appropriate only for certain demyelinating diseases, such as GBS. Petitioner does not have GBS. She does not have any demyelinating disease.

Moreover, Dr. Blitshteyn attempts to prove causation through a theory of challenge-rechallenge (sometimes known as positive rechallenge), i.e., petitioner's syncope occurred six days after her second Gardasil and again three weeks after her third Gardasil. But rechallenge usually manifests in a shorter onset interval after the subsequent vaccination (rechallenge). Here, the time period was longer (although petitioner's counsel whittled it down from three weeks to eight days in the second part of the hearing). Dr. Blitshteyn explains her reasoning that this constituted rechallenge because Madison had numerous episodes per day. But then Madison went one and one-half years without any episodes at all. Dr. Blitshteyn had no explanation for Madison's resumption of neurocardiogenic syncope 16 months after a symptom-free hiatus except to say that autoimmune diseases are known to relapse and remit. The undersigned is familiar with relapsing and remitting multiple sclerosis ("MS"), but petitioner does not have MS. Dr. Blitshteyn's reasons for her conclusion of causation do not instill confidence in the

undersigned as to their credibility: (1) neurocardiogenic syncope has not been well-researched; therefore Dr. Blitshteyn has to analogize to diseases petitioner does not have; (2) neurocardiogenic syncope is like POTS; (3) POTS is autoimmune-based; (4) other autoimmune diseases appear six days or three weeks after a trigger; (5) other autoimmune diseases can manifest rechallenge; and (6) other autoimmune diseases relapse and remit. Dr. Blitshteyn is implying that, since the basis for her causation conclusion can apply to other diseases, it must apply to neurocardiogenic syncope, an illness for which Grubb in his 2005 article (Exhibit 39) writes we know little concerning etiology. Petitioner cannot satisfy her burden of proof through speculation.

There may come a time when neurocardiogenic syncope is well-researched and someone has an explanation for its pathology, i.e., why it occurs and whether anything other than exertion, low fluids, low salt, stress, and a multiplicity of other non-medical factors, can cause it. That time has not occurred.

Moreover, Dr. Blitshteyn assumes that petitioner's autonomic nervous system is impaired rather than experiencing periodic abnormal responses to triggers. There is no reason for the undersigned to view petitioner's autonomic nervous system as impaired without proof. The hiatus of one and one-half years without symptoms casts in doubt Dr. Blitshteyn's assertion that petitioner's autonomic nervous system is impaired rather than experiencing episodes of disturbance. The undersigned found highly relevant the Grubb's statement that what distinguishes neurocardiogenic syncope from other diseases of orthostatic intolerance is that, between episodes, these patients complained of few (if any) autonomic symptoms. Ex. 39, at 3000. "Thus, in this group, the autonomic system appears to function in a relatively normal manner, despite being somewhat 'hypersensitive,' as opposed to other conditions in which the autonomic system appears to 'fail,' functioning at a level inadequate for the body's needs, which results in varying degrees of orthostatic intolerance." Id. In other words, between neurocardiogenic syncope episodes, the patient does not experience an impaired autonomic nervous system. The medical literature petitioner filed disputes Dr. Blitshteyn's theory that Gardasil has injured petitioner's autonomic nervous system. As Dr. MacDonald testified, the fact that petitioner is an active and accomplished student, earning A's in school, doing weight-lifting, running cross-country, and playing soccer and basketball, is not consistent with someone with an impaired autonomic nervous system,.

Respondent posits that petitioner's basilar migraine caused her neurocardiogenic syncope. Petitioner, not respondent, has the burden of proving a prima facie case. She has not satisfied her burden of proving the first prong of Althen. It is therefore unnecessary for the undersigned to issue a ruling on whether there is a known factor unrelated that caused Madison's neurocardiogenic syncope. Petitioner has failed to prove the first prong of Althen.

Prong Two of Althen

Since the undersigned rules that petitioner has failed to prove that Gardasil can cause neurocardiogenic syncope, the undersigned also rules that petitioner has failed to prove that Gardasil did cause her neurocardiogenic syncope in this case. Petitioner has failed to prove the second prong of Althen.

Prong Three of Althen

Petitioner relies heavily on the temporal intervals between her second Gardasil vaccination and the onset of her neurocardiogenic syncope (six days) and between her third Gardasil vaccination and renewed symptoms (three weeks, although arguably eight days). If this were a case of GBS or any demyelinating disease, this indeed would be appropriate timing to convey causation. However, since petitioner has failed to prove that neurocardiogenic syncope is an autoimmune disease to begin with, it is impossible to say what an appropriate time interval would be for causation.

There is an additional interval in this case—that of one and one-half years between the cessation of symptoms after the third Gardasil and the resumption of those symptoms--yet no one, including Dr. Blitshteyn, knows what caused the resumption of those symptoms. Dr. Blitshteyn said there was no trigger. She offered the explanation that autoimmune diseases are known to relapse and remit as if this satisfactorily explains the 16-month hiatus. This is speculation. Dr. Blitshteyn proffers her conclusion and then speculates it must be so because it happens to other people with diseases that petitioner does not have. Speculation is unacceptable as credible proof.

As the Slade article on postlicensure surveillance indicated, 90 percent of syncope following Gardasil vaccination occurred on the same day as vaccination, and half of those occurred within fifteen minutes of vaccination. Ex. 27, Tab I; Ex. A1. Six days after the second Gardasil is too late to be an appropriate temporal interval to connote causation to fit within the observation of the Slade and his co-authors. Three weeks or even eight days after the third Gardasil would be too late to be an appropriate temporal interval to connote causation to fit within the observation of the Slade article.

In addition, Dr. Blitshteyn says that Gardasil caused Madison's basilar migraine. According to Dr. Blitshteyn, Madison did not have migraine until a year after her neurocardiogenic syncope, which would make the onset interval between the second Gardasil and basilar migraine at one year. Dr. Blitshteyn does not explain the basis for her opinion that Gadasil can cause basilar migraine a year later. She testified that Madison's neurocardiogenic syncope and basilar migraine were co-morbidities unrelated to each other. Petitioner has failed to prove the third prong of Althen both for neurocardiogenic syncope and basilar migraine.

In sum, there are too many unknowns in this case, from understanding the medical theory underlying neurocardiogenic syncope (and there may be more than one explanation) to identifying all the triggers other than the obvious ones (exertion, low salt, dehydration, stress), and what timing is appropriate for causation. As Dr. Blitshteyn testified repeatedly, medical research of the etiology of neurocardiogenic syncope has not been done. Her testimony, therefore, is replete with analogies to other illnesses (POTS, GBS, ADEM), whose pathologies are well-known. But petitioner has none of these illnesses, and it is overly simplistic to say that because certain types of POTS may be autoimmune, neurocardiogenic syncope is therefore autoimmune. Petitioner has presented mere speculation, which the undersigned finds unpersuasive. Petitioner has failed to present a prima facie case.

This petition is hereby **DISMISSED**.

CONCLUSION

Petitioner's petition is **DISMISSED**. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court is directed to enter judgment herewith.[13]

IT IS SO ORDERED.

May 30, 2014
DATE

s/Laura D. Millman
Laura D. Millman
Special Master

[13] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party, either separately or jointly, filing a notice renouncing the right to seek review.