In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Case No. 11-442V

Filed: October 29, 2015

[TO BE PUBLISHED]

* *		
TABITHA PRICE, as Mother and Natural Guardian of D.P.,	*	
	*	Ruling on Entitlement; DTaP; MMR; Prevnar; Anaphylaxis; Neurological Injuries; Epilepsy; Seizures.
Petitioner,	*	
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *		

Clifford Shoemaker, Shoemaker and Associates, Vienna, VA for petitioner.
Robert Paul Coleman, III, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Gowen, Special Master:

On July 7, 2011, Tabitha Price ("petitioner") filed a petition on behalf of her minor son ("D.P." or "minor child") for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 – 34 (2012)[2] (the "Vaccine Act" or "the Program"). Petitioner alleged that as a result of receiving Diphtheria-Tetanus-acellular-Pertussis ("DTaP"), Measles-Mumps-Rubella ("MMR") and Pneumococcal Conjugate ("Prevnar") vaccines on August 4, 2008,

[1] Because this published ruling contains a reasoned explanation for the action in this case, I intend to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to delete medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

D.P. had a severe anaphylactic reaction within two minutes of the vaccinations, which caused him to suffer a grand mal seizure. Petitioner further alleged that several hours later D.P. experienced more seizures and subsequently developed a seizure disorder and secondary developmental delay.

In addition to documentary evidence in the form of medical records, petitioner presented the testimony of Yuval Shafrir, M.D., a neurologist and epileptologist. The respondent presented the testimony of Peter Bingham, M.D., a pediatric neurologist. Both parties submitted medical literature in support of their positions.

For the reasons stated herein, I find by preponderant evidence that: (1) the petitioner has presented a reasonable theory as to how D.P.'s vaccinations caused an anaphylactic reaction in the form of seizures, (2) she presented a logical cause and effect explanation relating the vaccinations to D.P.'s anaphylaxis and seizures, and (3) the timing in this case was particularly significant. Respondent's contention that the seizures occurred as a result of pure coincidental onset of idiopathic epilepsy within two minutes of receipt of the vaccines, or occurred as a result of an unknown gastrointestinal illness, for which there was no evidence, I find to be considerably less likely.

Accordingly, I conclude that D.P. is entitled to compensation under the National Childhood Vaccine Injury Act.

I. BACKGROUND

A. Procedural History

Petitioner filed numerous medical records in support of her petition. See Petitioner's ("Pet.") Exhibits ("Exs.") 1-28, 41-53. On April 19, 2012, respondent filed a Rule 4(c) report recommending against compensation. Respondent's ("Res.") Report at 9, docket no. 24, filed Apr. 19, 2012. Respondent argued that "petitioner [had] not offered a reliable medical opinion demonstrating that any of [the minor's] vaccinations either could be, or were, the cause of [the] alleged injury." Id. at 11. Additionally, respondent argued that "[t]he records submitted also [did] not contain a medical theory causally connecting the vaccinations and injury, nor [did] they provide a logical sequence of cause and effect showing that the vaccinations were the reason for the injury, as required by *Althen*." Id.; see *Althen v. Sec'y of HHS,* 418 F.3d 1274, 1278 (Fed. Cir. 2005).

On May 1, 2013, petitioner filed an expert report from Dr. Yuval Shafrir, along with his curriculum vitae and medical literature. See Pet. Exs. 29-40. Thereafter, a status conference was held on May 7, 2013, where the parties agreed to proceed with petitioner preparing a demand, in addition to respondent filing a responsive expert report. Order, docket no. 43, filed May 8, 2013. Petitioner filed a status report indicating her demand was conveyed to respondent on July 8, 2013. Respondent filed a responsive expert report from Dr. Peter Bingham, along with his curriculum vitae and medical literature on September 19, 2013. See Res. Exs. A-D.

A status conference was held on October 8, 2013, to discuss additional proceedings. The parties agreed to proceed with an entitlement hearing and were ordered to determine a hearing

date. Order, docket no. 53, filed Oct. 8, 2015. A hearing order was issued on November 12, 2013, scheduling an entitlement hearing for March 3 and 4, 2014, to take place in Washington, D.C. before Special Master Hamilton-Fieldman. Hearing Order, docket no. 54, filed Nov. 12, 2013. Petitioner filed pre-hearing submissions on January 7, 2014 and respondent filed her pre-hearing submissions on January 28, 2014. However, as a result of inclement weather, the entitlement hearing was cancelled on March 2, 2014.

Thereafter, in order to clarify conflicting evidence between the medical records and petitioner's assertions as to whether there was an incidence of vomiting in advance of the child's initial seizure, Special Master Hamilton-Fieldman ordered a fact hearing on whether the minor child had a gastrointestinal illness prior to his vaccinations. The parties were ordered to file a joint status report providing dates for a fact hearing, as well as any desired affidavits. See Order, docket no. 60, filed Mar. 11, 2014. On April 11, 2014, a fact hearing was scheduled for May 20, 2014 in Washington, D.C. See Pre-Hearing Order, docket no. 69, filed Apr. 11, 2014.

On April 10 and 14, 2014, petitioner's counsel filed affidavits from Ann Wilson, the minor child's grandmother; Nancy Floyd, the minor child's aunt; and Tabitha Price, the minor child's mother and petitioner in this matter. See Pet. Exs. 51-53. However, only Tabitha Price presented testimony at the fact hearing on May 20, 2014. See Transcript of Fact Hearing, docket no. 74, filed June 4, 2014. At the conclusion of the hearing, respondent was ordered to file a supplemental expert report based on the testimony at the fact hearing. See Order, docket no. 72, filed May 20, 2014. Additionally, the parties were notified that any findings of fact would be incorporated in an entitlement decision. Id.

An entitlement hearing was thereafter scheduled for September 19, 2014. See Prehearing Order, docket no. 77, filed June 30, 2014. On July 7, 2014, respondent filed a supplemental expert report from Dr. Bingham. See Res. Ex. E. Petitioner elected not to file a responsive expert report from Dr. Shafrir. See Pet. Status Report, docket no. 79, filed Aug. 4, 2014. On September 10, 2014, this case was reassigned to the undersigned. Subsequently, petitioner filed additional medical literature in support of her position. See Pet. Exs. 54-59.

An entitlement hearing was held on September 19, 2014, where Dr. Shafrir testified on behalf of petitioner and Dr. Bingham testified on behalf of respondent. See Transcript of Entitlement Hearing, docket no. 86, filed Oct. 8, 2014. Petitioner filed a post-hearing brief on November 7, 2014 and a reply brief on December 23, 2014. Respondent filed a post-hearing brief on December 5, 2014. Accordingly, this case is ripe for a decision.

B. Summary of the Facts

D.P. was born prematurely on April 13, 2007 at thirty-six weeks gestation, weighing six pounds fourteen ounces. Pet. Ex. 1 at 129. D.P. was delivered via cesarean section. Id. His mother's preoperative diagnoses included hypertension, failure to progress in labor, and failed induction of labor. Id. The pregnancy was complicated by low amniotic fluid and gestational diabetes. Id. at 30. Additionally, D.P.'s mother tested positive for a group B streptococcus

infection. Id. at 146. At birth, D.P.'s Apgar Scores[3] were nine and nine at one and five minutes old. Id. at 129. D.P. was discharged home with his mother after three days. Pet. Ex. 11 at 9.

Within the first year of life, D.P. had periodic issues with reflux, colic, vomiting, conjunctival infection with obstruction of his tear duct, umbilical hernia, and various upper respiratory infections, ear infections, and fevers. Pet. Ex. 7 at 23-50. On February 5, 2008, at ten months of age, D.P. was brought to a pediatric gastroenterologist for an evaluation due to gastrointestinal complaints. Id. at 112. His symptoms were described as "constipation problems and reflux symptoms." Id. The physician continued his Zantac prescription and deferred further evaluation. Id.

On August 4, 2008, D.P. was seen for his fifteen-month check-up by Dr. Nora Patonay at Conyers Pediatrics. Pet. Ex. 7 at 17. At this appointment he received DTaP, MMR and Prevnar vaccinations. Id. at 21. At 10:20 a.m., within two minutes of his vaccinations, D.P. suffered a seizure. Id. at 17, 20. An online VAERS report submitted by Conyers Pediatrics described the incident as follows:

> Patient given dtap #4, mmr #1, and prevnar #4. Two minutes after administration of vaccines patient began seizing. Seizure lasted for approximately 2-3 minutes. He was posturing and pupils were dilated, arms and legs shaking, lips and face were blue. We did treat with 5L of oxygen. Vitals were within normal limits and stable afterwards 128 [heart rate] and 32 resp/minute, o2 sat 98%. Valium prepared but not needed. 911 called and patient transported to Egleston Children's Hospital.

Id. at 20. Conyers Pediatrics documented that D.P. "became limp, turned blue, had grand mal seizure, jerking legs [and] arms" after receiving his immunizations. Id. at 17. The medical records further noted that oxygen was given to D.P., and in less than two minutes, his seizure stopped, and his lips and skin turned pink. Id. After the seizure, D.P. was moaning and limp. Id. at 18.

According to petitioner, on the way to Dr. Patonay's office, D.P. "was eating a hash brown and choked on it. It caused him to throw up the food that he was swallowing, but he was fine after that." Pet. Ex. 52 at 1-2; see also Pet. Ex. 18 at 47 (an emergency room record noting mom reported D.P. "eating a hash brown this am in [the] car and then vomited it out. She [was] not sure if he choked as he was in the backseat with his sister. No choking sounds heard."). Dr. Patonay noted that D.P. had no illness at the time of his vaccinations. Pet. Ex. 7 at 21.

D.P. was transported by ambulance to Children's Hospital of Atlanta-Egleston, with a triage time of 11:57 a.m. Pet. Ex. 18 at 48, 176. The triage notes indicate that D.P.'s presenting symptoms were seizure and that his respiratory effort was "easy," his skin color and temperature were normal for a child, he had a regular heart rate and rhythm, and he was sleeping, but arousable. Pet. Ex. 18 at 46. The emergency department physician noted that D.P. was "back to baseline,"

[3] "A numerical expression of the condition of a newborn infant, usually at 60 seconds after birth, being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." Dorland's Illustrated Medical Dictionary 1682 (32d ed. 2012) [hereafter "Dorland's"].

and that neurology services indicated that "no workup [was] necessary . . . ." Id. at 48. The physician further noted that "if there [was] another event[,] then the child will need [a] neuro clinic appointment." Id. D.P. was discharged at approximately 1:16 p.m. Id. at 50.

D.P.'s aunt, Nancy Floyd, brought him back to Egleston at 3:54 p.m. that same day, August 4, 2008, after D.P. suffered a second seizure in the car on the way home from the earlier hospital visit. Pet. Ex. 18 at 210. The medical record notes:

> Aunt reports that [patient] was at baseline on way home from ER smiling and talking. He then had emesis.[4] [Patient] then became fussy. Then within 15 minutes mom [sic][5] noted that he became stiff in all four extremities with possible shaking at the distal extremities. Eyes rolled back into head. Aunt unsure if any color changes. Episode lasted 2-3 minutes. [Patient] very tired afterwards and not responding. [Patient] did respond when EMS placed IV. Episode occurred around 2:45 today.

Id. at 210-11. A neurological assessment at the emergency department noted that "upon arrival to the room, [patient was] gazing, apneic, . . . placed on non-rebreather 100%". Id. at 85. Thereafter, D.P. experienced a third seizure which was observed by Dr. Shroff directly. Id. at 85, 213. D.P.'s third seizure lasted one minute, with tonic clonic movements, eye rolling, and breathing. Id. at 213. He was given Ativan as his seizing stopped. Id. D.P. was subsequently hospitalized for several days and experienced four more seizures in the course of his stay. Pet. Ex. 5 at 14.

Labs drawn at the time of the third seizure showed mildly low blood glucose at 57 L (range 65-100 MMOL/L), sodium at 133 L (range 136-145 MMOL/L), bicarbonate at 17 L (range 20-28 MMOL/L) and ammonia at 6 L (range 22-48 UMOL/L). Pet. Ex. 18 at 61. He was treated with a bolus of dextrose which rapidly returned glucose level to 89 L. Id. at 83. An EEG performed on August 5, 2008, indicated "[a]bnormal EEG with mild asymmetry of the background voltage and frequency. The left hemisphere [was] consistently slower and lower in voltage. The right hemisphere contain[ed] high-voltage posterior slowing." Id. at 70. Dr. Philip Holt believed the findings were nonspecific, but suggested diffuse neuronal dysfunction, likely more pronounced in the left hemisphere. Id. Further, he believed the "[f]indings may be metabolic, pharmacologic, infectious or even postictal." Id.

A head CT scan was negative. Pet. Ex. 18 at 83. A lumbar puncture showed no organisms, few white blood cells, and many red blood cells. Id. at 90. A brain MRI performed on August 5, 2008, noted multiple bilateral dilated perivascular spaces in the region of the basal ganglia. However, there was "no evidence of territorial infarction, hemorrhage, mass, mass effect or midline shift." Pet. Ex. 9 at 42. Dr. Denis Atkinson Jr.'s impression was that the MRI findings were normal and age appropriate. Id. Dr. Yong Park interpreted these films two years later, on

---

[4] "Vomiting." Dorland's, supra note 3 at 608.

[5] Petitioner's affidavit notes that her son, D.P., was in the care of her sister, Nancy Floyd, while she sought medical treatment at Eastside Medical Center for a spike in her blood pressure and a headache she experienced that day. Pet. Ex. 52 at 2-3.

August 20, 2010, and noted a "slight left temporal horn asymmetry, but no evidence of mesial temporal stenosis or cortical dysplasia." Pet. Ex. 5 at 14. D.P. was discharged from Egleston on August 7, 2008 with a diagnosis of seizure, asthma, and diarrhea. Pet. Ex. 18 at 34, 36. He was treated with Dilantin for his seizures. Id. at 62.

On November 20, 2008, D.P. was seen at Emory Pediatric Neurology at nineteen months of age. He was reported to be taking a small dose of Keppra, a seizure medication, by mouth twice a day. Pet. Ex. 4 at 48. His mother reported last seeing a staring spell approximately one month prior. Id.

On April 15, 2009, D.P. underwent an evaluation at Babies Can't Wait upon referral from his pediatrician due to concerns regarding his sensory response and history of seizures. Pet. Ex. 7 at 89. The evaluation noted that his seizures were well-managed, but that his mother had concerns about his sensory issues. Id. Specifically, petitioner reported that D.P. would "often fall and shake in response to loud noises, frustration, or concentrated tasks. He chew[ed] on non-food items and roll[ed] his eyes when his hair [was] being washed." Id. Also, he was a picky eater. Id. It was determined at that time that D.P.'s "general development did not appear to be adversely impacted by his sensory and neurological issues, as demonstrated by his scores . . . ." Id. Accordingly, he was not eligible for early intervention support. Id. at 84. D.P. was found to have shown "average developmental skills for his age," based on a review of his medical records and a multidisciplinary evaluation report. Id.

On April 21, 2009, D.P. was seen by a pediatric neurologist, Dr. Larry Olson, at Emory Children's Center. Dr. Olson noted that D.P.'s parents reported that "he has not had any 'more big events,'" but that D.P. experienced tremors in his hands and upper body "for a couple of seconds," and was responsive during those spells. Pet. Ex. 4 at 33. They also reported again that when water was poured on his head in the tub, D.P.'s eyes would roll back and he would "get rowdy." Id. at 33. He would get better when he was out of the water. Id. Dr. Olson noted that the developmental specialist at Babies Can't Wait found that D.P. was developmentally "'fine,'" but that the specialist did note sensory concerns. Id.

Dr. Olson further noted that D.P.'s family was "insistent that the vaccines have caused [D.P] trouble with seizures and developmental delays," and that "they [did] not want him to have any more vaccinations." Id. at 34. Dr. Olson recommended that they adhere to the CDC guidelines for vaccination, but that "it [was] ultimately up to the family and the pediatrician to discuss" his vaccination schedule. Id. He further assessed that "the spells where his eyes rolled back in the tub are probably not reflex seizures" but that the family should attempt to videotape them for future reference. Id. He also recommended an evaluation at Emory Autism Center and Marcus Autism Center. Id.

D.P. was evaluated at the Marcus Autism Center for pervasive developmental disorder on July 13, 2009. Pet. Ex. 3 at 3-18. Petitioner and several family members provided information for this evaluation; additionally, the evaluators reviewed D.P.'s medical records. Id. at 3. D.P.'s family reported that D.P.'s feeding habits changed and that he is a picky eater. Id. He had become very clumsy and fell a lot. Id. He also "started to turn his right foot in when he walk[ed] or [ran]," which

contributed to his falling. Id. "When he [gets] excited he flaps his hands" and "when in a new situation or around a lot of new people, he will shake all over." Id.

> Midway through the assessment, prior to moving to another testing room, [D.P.] was observed to fall and was unresponsive for several seconds. Initially it appeared as though he tripped over his grandmother's legs, however, his grandmother reported that he had gone limp. He appeared to quickly recover and easily transitioned to a different testing room. However, qualitatively, his interactions seemed to differ after this episode. For example, [D.P.] appeared more inattentive and distractible.

Id. at 11. It was further noted that D.P.'s eye contact was not "well meshed with his requests and smiles." Id. at 12. He was observed to be "somewhat repetitive" and appeared fixated on a particular toy. Id. "[H]is behavior was notably different when comparing his behavior from before his falling episode during informal free play and after the episode during a semi-structured play session." Id.

D.P.'s cognitive skills were described as "being in the low end of Average and at an age equivalent of 1 year, 10 months" (D.P. was 2 years and 2 months at this time). Id. at 13. His ability to coordinate visual and fine motor process was noted to be markedly weak. Id. "His pre-academic abilities, when compared to a child aged 2 years, 6 months, were found to be advanced." Id. at 16. He was below average for adaptive abilities, compared to other boys his age, and was in the average range for his socialization skills. Id.

A developmental diagnosis was not made at his evaluation at Marcus Autism Center. Id. at 17. He was referred to child psychology to address behavioral difficulties noted at home, and neurology to assess the status of his seizure control. Id. It was noted that a reevaluation at a later date was important "given that some of the symptoms associated with an autism Spectrum Disorder were denoted during the assessment such as atypical play and his early letter/number knowledge." Id. Additional recommendations included assessments in speech and language therapy, and a special needs pre-school coordinator for his county. Id.

On August 5, 2009, D.P. was seen for follow-up with his pediatric neurologist Dr. Larry Olson at Emory Children's Center. Pet. Ex. 4 at 18. In his consult note to Dr. Nora Patonay, Dr. Olson stated his impression was "presumed complex partial seizures" that persist with a frequency of one every other day, typically around 20 seconds, with behavioral arrest, minor finger automatisms bilaterally, often followed with brief limpness." Id. Dr. Olson increased the dosage of Keppra to 3 ml twice a day.

On February 1, 2010, D.P. underwent an EEG. The impression of his EEG was that the EEG was abnormal secondary to focal slowing and sharp activity over the left frontotemporal region suggestive of focal irritating focus. Pet. Ex. 5 at 195. On August 20, 2010, D.P. was admitted to the Medical College of Georgia for EEG monitoring because of staring that interrupted the flow of his activity, with unresponsiveness. Pet. Ex. 5 at 14. He was tapered off Trileptal and experienced no convulsive seizures while off his medication. Id. at 15. It was noted however, that after D.P. was completely off his medication they saw "epileptiform discharges that were diffuse

and bilateral, left greater than right." Id. There were no EEG changes during his staring spells. Id. The record notes that it was explained to D.P.'s parents that "while [D.P.] has a diagnosis of epilepsy with left-sided seizure focus, the episodes of staring . . . do not appear to be breakthrough complex partial seizures." Id. It was recommended that D.P. continue on his Trileptal at 6 ml twice a day and follow up in three months.

On Thursday, February 24, 2011, D.P. presented to the Egleston emergency department for increased absence seizures since Saturday, February 18, 2011. Pet. Ex. 18 at 139. Petitioner reported that the night before the emergency department visit, D.P. had five absence seizures, each lasting 2 minutes or less. Id. at 140. "He [had] also been saying strange things . . . with repeating phrases." Id. Petitioner reported that D.P. had nausea and vomiting, as well as an approximate 101 degree fever the night before he presented to the emergency department. Id. at 139. Nausea and vomiting were not present the day of the visit, but D.P. complained of forehead pain. Id. He was noted to be awake, alert, happy, smiling, and playful. Id.

D.P. was discharged with a diagnosis of viral illness and seizures. Id. at 142. Petitioner was instructed to have him follow up with a pediatrician and a neurologist. Id. It was noted that D.P.'s "seizure threshold appear[ed] to have decreased due to his current febrile illness." Id. "Given his sore throat symptoms, he may develop more symptoms of an upper respiratory infection in the next few days. He may also have more frequent seizures because of his viral illness." Id. Ibuprofen or Tylenol was prescribed, as needed. Id.

II. FACT RULING

Prior to the entitlement hearing before the undersigned, Special Master Hamilton-Fieldman held a fact hearing on whether D.P.'s spit up of a hash brown from Burger King in the backseat of his mother's car, on the drive to the pediatrician's office, where he received the vaccinations at issue on August 4, 2008, was evidence of a gastrointestinal illness or more likely a spitting up or choking on the hash brown.

At the fact hearing, Mrs. Price testified that her fourteen year old daughter and fifteen month old son, D.P., were in the back seat of the car that day. Fact Transcript ("Fact Tr.") at 19, docket no. 74, filed June 4, 2014. D.P. sat in a car seat. Fact Tr. at 10. On the way to the pediatrician's office, they stopped at Burger King because D.P. liked the little round hash browns they offered. Fact Tr. at 9. Mrs. Price testified that about ten minutes after leaving Burger King, she heard D.P. cough. Fact Tr. at 10. She looked in the rear view mirror and saw him spit out the hash brown he was eating. Fact Tr. at 10. She also saw her daughter grab a napkin and wipe away the hash brown. Fact Tr. at 20. Her daughter then said, "[he] spit it up, he didn't throw up." Fact Tr. at 20. Her daughter told her that D.P. coughed up the hash brown that he had just eaten. Fact Tr. at 32. According to Mrs. Price, after that incident D.P. was fine. Id. They continued to the doctor's office. At the doctor's office, D.P. played with a toy on the floor with his grandmother in the waiting room. Fact Tr. at 11. Dr. Patonay examined him and said that he was growing normally and had no illness. Fact Tr. at 11; see Pet. Ex. 7 at 21. Subsequently, D.P. suffered a seizure immediately after receipt of DTaP, MMR and Prevnar vaccinations. Pet. Ex. 7 at 20. Dr. Patonay noted in the VAERS report of that event that there was no illness at the time of vaccination. Id.

Medical records from D.P.'s emergency room visit after his seizure noted that petitioner reported D.P. was "eating a hash brown this am in [the] car and then vomited it out. She [was] not sure if he choked as he was in the backseat with his sister. No choking sounds heard." Pet. Ex. 18 at 47. At the fact hearing, petitioner was cross-examined on the fact that she either used the word "vomited" when she was describing this event, or that the word was used by the physician taking the history. Petitioner testified that she might have said vomited because she prefers to use that instead of "spit up" or "throw up." Fact Tr. at 20.

At the outset of the entitlement hearing, after I had read the fact hearing transcript and ascertained from the parties at the entitlement hearing that there would be no further testimony on this point, I advised the parties of my conclusion that the evidence shows D.P. spit up the hash brown that he had just eaten, and that there was no evidence of vomiting abdominal contents. Entitlement Transcript ("Tr.") at 52, docket no. 86, filed Oct. 9, 2014.

III. EXPERT OPINION AND CAUSATION ANALYSIS

A. Issues to be determined

Petitioner requests that I determine: (1) whether D.P. suffered an anaphylactic reaction to the vaccines in the form of a seizure immediately after receipt of the vaccines; and (2) whether, as a result of the seizure, D.P. suffered an encephalopathy or brain damage and has had continuing impairment from that injury. Tr. at 53-54. Respondent requests that I determine: (1) whether the petitioner has met her burden to show causation under *Althen*; or in the alternative, (2) whether D.P.'s condition was caused by viral gastroenteritis. Id. at 53.

B. Legal Standard

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of HHS*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

In order to prevail under the Program, a petitioner must prove either a "Table" injury or that a vaccine listed in the Table was the cause-in-fact of an injury (an "off-Table" injury). Petitioner alleges D.P. suffered from anaphylaxis, causing seizures, and encephalopathy. The facts do not support the Table definition under the QAI of encephalopathy. However, after analysis of the evidence, I have concluded that the petitioner did prove a Table Anaphylaxis—the anaphylaxis having occurred within the required four hours of receipt of the DTaP and MMR vaccinations.[6] Additionally, petitioner has proved as by preponderant evidence that D.P. suffered ongoing seizures secondary to the anaphylactic injury and is therefore entitled to compensation.

[6] The Vaccine Injury Table, 42 C.F.R § 100.3 lists anaphylaxis or anaphylactic shock occurring within four hours of DTaP and MMR vaccinations as table injuries.

An "off-Table" injury is initially established when the petitioner demonstrates, by a preponderance of the evidence that: (1) the minor child received a vaccine set forth on the Vaccine Injury Table; (2) he received the vaccine in the United States; (3) he sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) the condition has persisted for more than six months. § 13(a)(1)(A).

There is no dispute but D.P. received the DTaP, MMR and Prevnar vaccines in the United States at the office of his pediatrician on August 4, 2008 in Atlanta, Georgia. He has also continued to experience symptoms in the form of additional seizures and a developmental delay for more than six months.

The respondent contended that D.P. did not experience anaphylaxis, and thus this case was presented as a cause-in-fact case. To satisfy her burden of proving causation in fact, petitioner must establish each of the three *Althen* factors by preponderant evidence: (1) a medical theory causally connecting the vaccination and the child's injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen*, 418 F.3d at 1278; see *de Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y of HHS*, 100 Fed. Cl. 119, 132 (2011), aff. per curiam, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See *Moberly v. Sec'y of HHS*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of HHS*, 931 F.2d 867, 873 (Fed. Cir. 1991).

The Federal Circuit in *Althen* noted that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a sequence hitherto unproven in medicine, 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." *Althen*, 418 F.3d at 1280.

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of HHS*, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280.

In determining whether petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether

petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury . . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of HHS*, 569 F.3d 1367, 1380 (Fed. Cir. 2009).

C. Expert Qualifications

1. Petitioner's Expert, Yuval Shafrir, M.D.

Dr. Yuval Shafrir is board certified in neurology with a special qualification in child neurology. Tr. at 57. He is also board certified in clinical neurophysiology. Id. He completed a fellowship in pediatric epilepsy and electroencephalography ("EEG"). Tr. at 57. He testified that he was board certified in pediatrics, but this certification "was time-limited, so he did not recertify after 1998." Id. He received his medical degree, magna cum laude, from the Sackler School of Medicine in Tel Aviv in 1982. Pet. Ex. 30 at 1. After medical school, he spent several years completing a pediatric residency in Israel and at North Shore University Hospital, a major affiliate of Cornell University Medical College. Id. Subsequently, Dr. Shafrir completed a pediatric neurology fellowship at Washington University in St. Louis and an epilepsy fellowship at Miami Children's Hospital. Id.; Tr. at 56. He worked as a pediatric neurologist at Walter Reed Army Medical Center, then at Georgetown University Hospital, and is currently in private practice. Pet. Ex. 30 at 1-2; Tr. at 56. At the hearing, Dr. Shafrir described himself as an epileptologist, which he explained is someone who specializes in epilepsy in children and in EEG. Tr. at 157. He is also an Assistant Professor in the Department of Pediatrics at the University of Maryland School of Medicine in Baltimore, Maryland. Pet. Ex. 30 at 1. He regularly treats children with epilepsy. Tr. at 109.

2. Respondent's Expert, Peter Bingham, M.D.

Dr. Peter Bingham is a board certified pediatric neurologist with seventeen years post-residency experience in general child neurology. Res. Ex. A at 1. He trained at Columbia College of Physicians & Surgeons and did his residency at the University of Pennsylvania and Children's Hospital of Philadelphia. Id.; Tr. at 115. Subsequently, he performed a two-year fellowship in neuromuscular disease and neurogenetics. Tr. at 115. Dr. Bingham continued on the faculty at the University of Pennsylvania and then to the University of Vermont. Tr. at 115. He is licensed to practice in the State of Vermont. Tr. at 115. He indicated that he currently reviews numerous medical journals and has authored articles in peer-reviewed journals. Tr. at 116-17.

Dr. Bingham testified that he works at the University of Vermont and the affiliated Fletcher Allen Hospital. Tr. at 116. He works predominately as a clinician, generally seeing child neurology cases, both outpatient and inpatient. Tr. at 117. About twenty to twenty-five percent of his time at the University of Vermont is devoted to research. Id. Dr. Bingham estimated that he treats approximately twenty infants and children each week. Id. He estimated that he has treated in the range of 1500 to 2000 patients with a seizure disorder. Id. The court granted respondent's request

that Dr. Bingham be offered as an expert in the field of pediatric neurology, to which petitioner did not object. Tr. at 117-18.

D. *Althen* Analysis

In this case, I have reviewed the medical records of D.P., the reports of the parties' respective experts, all of the testimony, and the medical literature submitted. Petitioner submitted two entire textbooks regarding allergy and anaphylaxis, among other literature. While I did not read all of the textbooks, I have read all chapters which appear to have relevance to this matter, in addition to the other literature submitted by both parties.[7]

i. *Althen* Prong One – Medical Theory

a. Petitioner's Expert Dr. Shafrir

Dr. Shafrir opined that D.P. suffered a cerebral anaphylaxis as a result of receiving DTaP, MMR and Prevnar vaccines on August 4, 2008. Tr. at 58. He testified that he considered this to be a "focal" cerebral anaphylaxis based upon the localized abnormalities on the EEG that was done the following day. Tr. at 60.

Dr. Shafrir described his differential diagnosis, saying that whenever you have "an acute appearance of dramatic clinical symptoms after introduction of a foreign antigen, especially with *the injection* of a foreign antigen, we have to assume that the patient has anaphylaxis." Tr. at 62 (emphasis added). As agreed by Dr. Bingham, anaphylaxis is defined as "an acute allergic phenomenon." Tr. at 127. Dr. Bingham opined that "there are people with all kinds of allergies where they can have a sudden, life threatening event, from an exposure to an antigen, be it dietary or a vaccination or sometimes it is unclear what the inciting event may be." Tr. at 127.

The term "anaphylaxis" is more formally defined in petitioner's exhibit 40:

> Anaphylaxis is a generalized, immediate IgE-mediated hypersensitivity reaction to a foreign antigen such as a protein, a hapten, or a polysaccharide. In susceptible persons, initial exposure to an antigen results in the formation of specific IgE

[7] Petitioner submitted the textbook, LIEBERMAN AND ANDERSON, ALLERGIC DISEASES: DIAGNOSIS AND TREATMENT (3d ed. 2007) [hereinafter "LIEBERMAN AND ANDERSON"] as exhibit 40. The chapters reviewed from that book include: Chapter 1, "Allergic Disease," by Akan and Lemanske; Chapter 5, "Anaphylaxis," by Kagy and Blaiss; and Chapter 16, "Allergic and Allergic like Reactions to Drugs and Other Therapeutic Agents," by Anderson.

Petitioner also submitted the textbook, CELSO PEREIRA, ALLERGIC DISEASES- HIGHLIGHTS IN THE CLINIC, MECHANISMS AND TREATMENT (2012) as exhibit 33. The chapters reviewed from that book include: Chapter 7, "Anaphylaxis," by Gelnick; Chapter 19, "Specific Immunotherapy and Central Immune System," by Tavares and Botelho; and Chapter 25, "Derived Products of Helminths in the Treatment of Inflammation, Allergic Reactions and Anaphylaxis," by Araujo and Soares.

> antibodies to that antigen. These antibodies attach to receptors on the surface of mast cells and basophils. This leads to changes in the cell membrane with degranulation and release of preformed chemical mediators and generation of new potent mediators. It is these mediators that produce the clinical symptoms of anaphylaxis.

Pet. Ex. 40 at 61.[8]

Dr. Shafrir testified that this case presented an anaphylactic phenomenon producing seizures in a child who had been previously sensitized to the gelatin in the DTaP and MMR vaccines, as well as to the pertussis antigen itself, by earlier vaccinations. Tr. at 70. He testified that in a patient with some underlying vulnerability, the sensitization by a prior vaccination causes the formation of IgE antibodies, which then become attached at the Fc receptor to other immune cells known as mast cells, which are located in the brain, as well as in the skin, the lungs, and gastrointestinal mucosa. Tr. at 70-71. When the child is exposed to the same antigen, through a subsequent vaccination, the previously sensitized IgE cells, attached to mast cells, cross link on the membrane and cause the mast cells to degranulate or dump their components, including histamines, leukotrienes, serotonin and cytokines, into the surrounding tissue in the brain, which results in a rapid anaphylactic reaction. Tr. at 70-71, 100. He supported this theory by reference to multiple articles regarding IgE and mast cells including the Kaigy and Blaiss chapter quoted above.[9]

The two-step mechanism of IgE-mediated anaphylaxis was explained in the Alan and Lemanske chapter in petitioner's exhibit 40. A susceptible person who has a predisposition to develop IgE antibodies to a specific antigen is initially sensitized by exposure to that antigen. Pet. Ex. 40 at 13.[10] Then upon subsequent exposure to the same antigen, the person can rapidly experience symptoms ranging from rhinorrhea to death. Id. The petitioner's expert also explained that anaphylactic reactions are often biphasic, with symptoms recurring, despite appropriate treatment, within two to eight hours of the initial rapidly occurring event. Id. at 65.

In this case, Dr. Shafrir noted that D.P. received his fourth DTaP vaccination and that both the DTaP and the MMR vaccines he received on August 4, 2008 contained gelatin. According to Dr. Shafrir, both the pertussis antigen in the DTaP and the gelatin in both vaccines have been implicated in anaphylactic reactions to vaccines. Tr. at 64. He opined that in this case, both the antigens in the vaccine and in the gelatin could cross the blood-brain barrier attached to IgE receptors on the mast cells in the brain, cause a cross linking of those mast cells in the brain, and produce the rapid release of the anaphylactic agents (histamines, leukotrienes, peptides and

---

[8] Kagy and Blaiss, Anaphylaxis 61 (2007) in LIEBERMAN AND ANDERSON.

[9] See also Katherine M. Nautiyal, Mast Cells Affect Brain Physiology and Behavior 18 (Columbia University 2011) [Pet. Ex. 39] (indicating, among other things, that a mast cell may contain up to 1000 granules which are stored and are ready for immediate release into the surrounding tissue upon activation by the IgE).

[10] Akan and Lemanske, Allergic Disease 13 (2007) in LIEBERMAN AND ANDERSON.

cytokines) in the mast cells. Tr. at 100. He testified that this reaction occurs within five minutes. Id. He further testified that D.P.'s initial seizure occurred as a result of the aforementioned mechanism, and that the subsequent seizures, beginning a little over four hours later, are explained by a secondary or biphasic hypersensitivity reaction that is not the immediate anaphylactic reaction. Id. Dr. Bingham agreed that whatever caused the initial seizure in D.P. caused all the ones that followed. Tr. at 160.

Dr. Shafrir's explanation of the role of IgE and mast cells in anaphylaxis is consistent with that provided by Kagy and Blaiss:

> Mast cells are marrow-derived, tissue resident cells that are essential for IgE mediated inflammatory reactions . . . . Mast cells express on their surfaces large numbers of high affinity Fc receptors for IgE. Therefore, the surface of each mast cell is coated with IgE molecules that have been absorbed from the circulation and serve as receptors for specific antigens. When antigens bind to the mast cell's surface IgE molecules, it undergoes activation that leads to its subsequent degranulation and release of granule contents into the surrounding tissues. The granules contain large amounts of histamine and other inflammatory mediators. Histamine is a major mediator of anaphylaxis.

Pet. Ex. 40 at 61.

Dr. Shafrir's implication of the gelatin in some vaccines including the DTaP and MMR vaccines received by D.P. on August 4, 2008 as the most likely stimulant of the anaphylactic reaction was supported in "Allergic and Allergic-Like Reactions to Drugs and Other Therapeutic Agents," by John Anderson M.D. which stated:

> Although infrequent, systemic allergic reactions, do occur to vaccines. Most of these reactions are now felt to be a result of IgE antibodies directed against porcine gelatin used as a stabilizer in these vaccines. Gelatin is found in various amounts in measles, mumps and rubella (MMR), varicella, rabies Japanese encephalitis, influenza and DTP vaccines.

Pet. Ex. 40 at 304.

While acknowledging Dr. Bingham's contention that seizures are not the most common manifestation of anaphylaxis and are in fact relatively uncommon, Dr. Shafrir provided several articles indicating that seizures occurred between one and two percent of anaphylactic presentations. One of such articles, from the Communicable Disease Control Immunization Program in British Columbia, was devoted to the discussion of anaphylactic reactions to vaccines. See generally Pet. Ex. 54.[11] That article stated that seizures occur in one to two percent of

[11] BC Centre for Disease Control, Communicable Disease Control Immunology Program, Section V – Management of Anaphylaxis in a Non-Hospital Setting (April 2013) (citing The Diagnosis and Management of Anaphylaxis: An Updated Parameter, 115 J. of Allergy and Clinical Immunology S483-523 (2005).

anaphylactic events. Id. at 3. Another article in the American Family Physician discussed the diagnostic criteria for anaphylaxis generally and stated that seizures occur in about 1.5 percent of the presentations. See Pet. Ex. 32 at 2.[12] The aforementioned Kagy and Blaiss chapter listed neurological symptoms of anaphylaxis, including dizziness, weakness, syncope, and seizures. Pet. Ex. 40 at 64.

In response to cross-examination as to the presence of the most common manifestations of anaphylaxis in D.P., which respondent's exhibit D notes are cutaneous, respiratory and cardiovascular in nature,[13] Dr. Shafrir noted that D.P. immediately turned blue, meaning he was cyanotic, and was emergently treated with five liters of oxygen, which signals that he could have experienced a respiratory symptom, or his symptom could have been secondary to the seizure. Tr. at 87-88. Dr. Shafrir noted that cyanosis is a sign of hypoxemia, a symptom commonly associated with anaphylaxis as noted in exhibit D. Tr. at 90; see Res. Ex. D at 256. He further testified that D.P. also collapsed and was hypotonic, additional symptoms of anaphylaxis noted in exhibit D. Tr. at 91; see Res. Ex. D at 256; see also Pet. Ex. 7 at 17 (noting D.P. was transported to hospital because was still moaning and limp after the seizure stopped). A red macular rash on D.P.'s left lateral lower extremity with a one centimeter blanching macule was noted when D.P. returned to Egleston Hospital after his second seizure that day. Pet. Ex. 19 at 178. Neither expert opined on the significance of this finding.

In response to questioning about whether the peripherally administered vaccine antigens could cross the blood-brain barrier and enter the brain causing anaphylaxis, Dr. Shafrir supplied literature regarding bee and wasp stings. See Pet. Exs. 34-38. The literature demonstrated that a single sting to a person who has been sensitized by a previous sting could cause a severe and life threatening reaction in the brain by way of an immune mechanism, without evidence of other more common symptoms of anaphylaxis, such as urticaria or respiratory symptoms. Tr. at 130. Dr. Shafrir contrasted this scenario with a situation where the person sustained massive stings at one time and succumbed to the effect of the venom. Tr. at 102. In a particularly cogent study from Hungary, in which there were forty-two victims of a bee sting, thirty had central nervous system reactions which included convulsions. The authors stated:

> The pathophysiological basis for anaphylaxis is the release of histamine, serotonin and other pharmacologically active substances by the Hymenoptera (bee or wasp) antigens from the mast cells and circulating basophils sensitized by IgE type homocytotropic immunoglobulins. In spite of earlier views, mast cells are present throughout the brain.

Pet. Ex. 38 at 3.[14]

---

[12] Angela W. Tang, A Practical Guide to Anaphylaxis, American Family Physician 2 (2003).

[13] See Kirk H. Waibel, Anaphylaxis, 29 Pediatrics in Review 255-56 (2008) [Res. Ex. D at 255].

[14] I. Meszaros, Transient Cerebral Ischemic Attack Caused by Hymenoptera Stings: the Brain as an Anaphylactic Shock Organ, 25 European Neurology 248-52 (1986).

The wasp sting analogy explaining the central nervous system reaction to an antigen to which a person was previously sensitized was also recognized in a case report of a man found in status epilepticus after a single wasp sting. See Pet. Ex. 34 at 1.[15] There were no rash or cardiovascular symptoms. Id. However, tryptase released from mast cells supported a diagnosis of significant anaphylaxis. Id. By history, it was found that anaphylaxis resulted from priming three weeks earlier. Id.

Dr. Shafrir testified that other potential explanations on the differential, beside an anaphylactic reaction to the vaccines, would include a breath holding spell, for which there was no evidence in this case, or causation by something the child already had, for which there was also no evidence and would be pure chance. Tr. at 60-61; see Pet. Ex. 29 at 26 (Dr. Shafrir noting that seizures associated with a breath holding spell or vasovagal reaction would be shorter and not associated with more seizures subsequently). He recognized that coincidence could possibly occur, but that the chances of that in the scenario presented here would be extremely small. Id. at 108. He said that in a situation where an extreme reaction occurs within two minutes of an injection of a foreign antigen that is known to cause side effects and anaphylaxis, pure chance would not be a serious consideration. Id. He testified that there are really no other mechanisms that would cause such a "dramatic and shocking" reaction as experienced by D.P within two minutes, other than anaphylaxis. Tr. at 73-74. In short, he maintained that D.P's response was dramatic and compelling, occurring just two minutes after the vaccines were administered, and that under these circumstances, the diagnosis is anaphylaxis until proven otherwise. Tr. at 83-85. Further, the timing of this event can be explained by his prior sensitization from earlier DTaP vaccinations, and by exposure to the porcine gelatin from prior vaccinations; whereby, re-exposure on the day of the event caused a rapid IgE and mast cell response causing anaphylaxis and repeated seizures and encephalopathy. Tr. at 69-72.

Ultimately, Dr. Shafrir testified that based primarily on the clinical picture and the EEG, D.P. suffered a brain anaphylaxis that affected the left hemisphere more than the right. Tr. at 112-13. This resulted in an encephalopathy and epilepsy for which he continues to be treated. Id. at 59-60. There was no evidence of a genetic cause of his epilepsy, and the hospital looked at multiple other causes, such as infections, through blood work, cerebral spinal fluid, and stool samples. Tr. at 112-13. The hospital ruled them out. Id. He testified that D.P.'s mildly low glucose commonly occurs after seizures, but is not the cause. Id. at 78-80; see Pet. Ex. 47 at 89 (noting "low glucose may have been related [to D.P.'s seizure], but an additional seizure occurred after the glucose was corrected," refuting any suggestion of a causal role). Dr. Shafrir further testified that the mildly low glucose and sodium levels, as well as ketones in the urine, were likely the result of the child not having been fed for a number of hours by the time he was re-hospitalized and his blood was drawn. Tr. at 80-81. He testified that young children do not have much metabolic reserve and if they are not fed, they can readily develop a low glucose level. Id.

b. Respondent's Expert Dr. Bingham

[15] Warner, et al., MRI Brain Appearances in Anaphylaxis: Novel Observation to Differentiate from Global Hypoxic Insult, 88 Supp. S2 Journal of Neurosurg Psychiatry A21 (December 2012).

The heart of the parties' disagreement is in the understanding of symptoms attributable to an anaphylactic reaction from an injection of a foreign antigen, such as a vaccine. Dr. Shafrir and Dr. Bingham agreed that vaccines can trigger an anaphylactic response. Tr. at 101, 148.

Dr. Bingham agreed that the timing of the initial seizure was definitely important and demanded a detailed accounting of the associated signs and symptoms, but he did not find the timing as compelling as Dr. Shafrir. Tr. at 125-26. Dr. Bingham believed the most common presentations of anaphylaxis, including cutaneous, respiratory, or cardiovascular symptoms, were not present in this case, and he did not believe that seizures could be part of an anaphylactic phenomenon. Id. at 127-30. He opined that there was not significant medical literature associating vaccines with epilepsy. Id. at 120, 130-31.

Dr. Bingham discussed D.P.'s low glucose (57), diarrhea, and other signs, as evidence of a viral gastroenteritis; but also stated that these were more proximal factors, not causal factors in the seizures. Tr. at 122-23. In other words, Dr. Bingham believed that these symptoms were associated with the seizures but not causative. Id. at 123. He said that it was an open question as to how viral gastroenteritis could cause seizures, but that it is seen. Id. at 123. He did not associate the changes in blood chemistry, including low glucose, slightly low sodium, low bicarbonate, and high specific urine gravity, to anaphylaxis. Id. at 125-27. Dr. Bingham opined that D.P. had idiopathic complex partial epilepsy that coincidently started on the date of vaccination and that the first seizure was most likely precipitated by viral gastroenteritis. Id. at 120. He agreed with Dr. Shafrir that idiopathic does not mean that there is no cause. Id. It is just that the cause is not understood. Id.

Dr. Bingham anchored his opinion in epidemiology. Tr. at 120, 167. He agreed that there was no doubt that vaccines can cause anaphylaxis. Tr. at 148. But, he thought the epidemiology was lacking to show that vaccines can cause epilepsy. Id. at 120. He testified that the incidence of the onset of epilepsy is higher in children between one and fifteen months of age relative to the incidence in later stages of life. Id. at 121. He said that the incidence of epilepsy in this age group is about one in a thousand, and about one third of those are idiopathic and the rest have identifiable causes. Id.

On cross-examination, Dr. Bingham was questioned about the statistical likelihood that an idiopathic epilepsy could occur within two minutes of a vaccination. In other words, how likely was it that the onset of epilepsy could occur within two minutes of vaccine administration in a child of this age group without having a causal relationship to the vaccine? Tr. at 136-40. Dr. Bingham agreed that based upon his figures of a one in a thousand incidence of epilepsy occurring in this age group, and one third of those being idiopathic, the overall likelihood of idiopathic epilepsy occurring during these fifteen months of age was 0.00067 percent. Id. at 139. He agreed that there are approximately 450 days in fifteen months, 10,800 hours, and 648,000 minutes in that same time period. Id. at 139-40. He agreed that a child would be exposed about five times to the first two minutes after vaccine administration in that time period. Id. at 140. Based on that, he agreed that it was plausible that the risk of the onset of idiopathic or unexplained epilepsy occurring within two minutes of a vaccine would be 0.0000000154321 percent, or less than a one in fifty million chance. Id. On later questioning, Dr. Bingham said that there would be three new cases of

epilepsy a day, and at some point one would probably occur in a doctor's office, but he recognized that it would be statistically rarer the more tightly defined the time period was. Id. at 166.

Ultimately, he said he was relying on epidemiology which has not identified a signal that would, for example, raise the relationship between a vaccine and the onset of epilepsy from 1.00 to 1.20. Tr. at 167. He agreed that epidemiology does not tend to be effective in identifying rare events, and that most papers would say that they were not sufficiently powered to identify a rise from something like 100 to 110 in 100,000. Id. at 167-68. He further agreed that in fact the identification of a rare case by epidemiology would require a study powered to identify a rise from something on the order of 100 to 100.1. Id.

Dr. Bingham thought that the spitting up incident in the car might suggest the onset of a gastrointestinal illness, but agreed that there was no other evidence specific for a gastrointestinal illness, and that many viral or bacterial causes for D.P.'s seizures were ruled out by testing. Tr. at 142-44. He thought D.P.'s low glucose and sodium, measured in the afternoon of August 4, 2008 at Egleston Hospital, may have suggested a gastrointestinal illness. Id. at 122-23. But, as Dr. Shafrir explained, a child of that age who has not eaten can have low glucose and sodium. Tr. at 80-81. Neither expert appeared to attach great significance to those results. The mildly low glucose was rapidly corrected with a bolus of dextrose and the child indeed suffered an additional seizure after his glucose level returned to normal. See Pet. Ex. 47 at 89.

As noted in respondent's exhibit D, an idiopathic anaphylaxis is a diagnosis of exclusion. Res. Ex. D at 257. Dr. Bingham essentially testified that it is not uncommon to make a diagnosis of a viral illness caused by some pathogen when one does not know which virus, and when lab results fail to identify a particular organism. Tr. at 161. Here, he agreed that there was no evidence of a viral encephalitis and that multiple known bacterial or viral causes were ruled out. Tr. at 142-44, 170.

Dr. Bingham further agreed that the petitioner's theory that D.P. may have had a pre-disposition to a seizure disorder that was triggered by the vaccines, and that this triggering often involves an immune-mediated event, was logical and plausible—even though he thought that, in medicine, there is sometimes a difference between logic and experience. Tr. at 142.

c. Analysis of *Althen* Prong One

Petitioner's burden under *Althen's* prong one is to present by preponderant evidence a reliable medical theory to explain how the vaccines in question could cause the illness and injury suffered by the petitioner's child. See *Althen*, 418 F.3d at 1278. Dr. Shafrir indeed presented a reasonable and persuasive theory that D.P. suffered a severe anaphylactic reaction to the DTaP and MMR vaccines. In particular, he proposed that the gelatin used as a stabilizer in these two vaccines was the likely inciting antigen. He also proposed that the pertussis antigen in the DTaP vaccine could have had the same effect in causing an anaphylactic response. The child had been exposed to both the gelatin and the pertussis antigen in prior vaccinations, thus likely causing him to have primed IgE antibodies attached to mast cells in the brain.

While seizures are an unusual manifestation of anaphylaxis, which is itself a rare reaction to vaccines, Dr. Shafrir's opinion that they do occur in one to two percent of anaphylactic events was supported in the submitted literature as described above. See Tr. at 72; Pet. Ex. 54 at 3. Dr. Shafrir also presented a logical explanation of the mechanism giving rise to the seizures immediately after receipt of the vaccines. He explained that anaphylactic reactions in the central nervous system are generally caused by the triggering of degranulation of mast cells that are present in the brain. As he testified, and as was well supported in the literature, upon exposure to a particular antigen some people develop IgE antibodies rather than the IgG or IgM when class switching occurs. Pet. Ex. 40 at 15-17. IgE causes that person to have an allergic response to a subsequent exposure to that same antigen. Id. at 60-61; Tr. at 70-71. The anaphylactic, or severe allergic response, occurs when a person is re-exposed to an antigen to which he has previously developed IgE antibodies. Id. In this case, D.P. was in all likelihood primed by prior receipt of the DTaP vaccine and vaccines containing porcine gelatin as a stabilizer. Tr. at 64. When he received his fourth DTaP and MMR vaccine containing gelatin on August 4, 2008, his system had been primed by the prior vaccinations. See Pet. Ex. 7 at 20; Tr. at 70.

Mast cells are present in numerous parts of the body including the brain. Tr. at 70-71; Pet. Ex. 39. Their surfaces are heavily populated with Fc receptors for IgE. Tr. at 70. When a child has been primed by prior exposure to an antigen and developed IgE antibodies to that antigen, the surface of his mast cells are coated with the IgE antibodies to that same antigen. Id. at 70-71. When he is re-exposed, as in this case, by a subsequent vaccination of the same type or containing the same stabilizer, the mast cells are triggered by the IgE antibodies to respond very rapidly to the new exposure to the antigen. Id. When triggered, the mast cells degranulate or dump hundreds of inflammatory molecules including histamines, leukotrienes, cytokines, tryptase and others into the surrounding tissue. Tr. at 100. Dr. Shafrir explained that D.P.'s rapid central nervous system response was caused by the degranulation of the brain resident mast cells into the surrounding brain tissue causing seizures. He supported this explanation by analogy to literature regarding central nervous system anaphylactic response to wasp and bee stings. He explained, as did the literature he provided, that a single bee or wasp sting on the periphery can cause a central nervous system anaphylaxis when the stung person was previously stung by a bee or wasp. Tr. at 65-67. The prior sting generated the IgE response and primed the mast cells to respond in rapid fashion at the time of a subsequent sting. The submitted literature described victims in status epilepticus and those that went into coma and died as a result of a single bee sting that occurred subsequent to an earlier priming sting. Id.; see Pet. Ex. 34 at 1; Pet. Ex. 37 at 1-2. This was distinguished from the situation where a person is stung simultaneously by many bees or wasps and succumbs to the venom from the stings. Tr. at 102-03.

ii. *Althen* Prong Two – Logical Sequence of Cause and Effect

Proof of *Althen* prong two requires a logical explanation as to how the vaccine did cause the injury in the petitioner. "A logical sequence of cause and effect' means what it sounds like—the claimant's theory of cause and effect must be logical." *Capizzano*, 440 F.3d at 1326. The proof need not rise to the level of scientific certainty but rather to the Vaccine Act's preponderance standard under the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.'" *Andreu*, 569 F.3d at 1378. A treating physician may rely on the close temporal proximity between a vaccine and an injury in concluding that there is a

logical sequence of cause and effect between the vaccine and the injury. *Capizzano*, 440 F. 3d at 1326. "Requiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." Id. at 1325-26.

Differential diagnosis is a well-accepted medical methodology for determining diagnoses and causation. It has been accepted by multiple courts under a *Daubert* analysis. The Third Circuit addressed the reliability of differential diagnosis as a method for assessing causation. The court held:

> We have recognized that differential diagnosis is a technique that involves assessing causation with respect to a particular individual, *In Re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 758 (3d Cir. 1994). Differential diagnosis is defined for physicians as "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings." Stedman's Medical Dictionary 428 (25th ed. 1990). The elements of a differential diagnosis may consist of the performance of physical examinations, the taking of medical histories, and the review of clinical tests, including laboratory tests. A doctor does not have to employ all of these techniques in order for the doctor's diagnosis to be reliable. See *Paoli*, 35 F.3d at 759. A differential diagnosis may be reliable with less than all the types of information set out above. See id. Indeed as we held in *Paoli* to the extent that the district court concluded otherwise [i.e. that a differential diagnosis made on less than all types of information cannot be reliable] we hold that it abused its discretion . . . . As noted by this court in *Paoli*, evaluation of the patient's medical records is a reliable method of concluding that a patient is ill even in the absence of a physical exam.

Kannankeril v. Terminix, 128 F.3d 802, 807-08 (3d Cir. 1997); see also *Hocraffer v. Sec'y of HHS*, 63 Fed. Cl. 765, 777 n. 15 (2005) (Judge Firestone noting that "[d]ifferential diagnosis or differential etiology has been accepted as reliable under the standards set forth in *Daubert* [and] by virtually every United States Court of Appeals to consider the issue" (internal citations removed)).

Dr. Shafrir's differential diagnosis of an anaphylactic reaction to the vaccinations was both reasonable and persuasive. He provided a logical cause and effect explanation of the mast cell mechanism that likely resulted in a central nervous system anaphylaxis in a child who received vaccine antigens to which he had previously been exposed from prior vaccinations of the same type. D.P. was tested for most, if not all, of the likely pathogenic organisms that could conceivably give rise to seizures, and all were negative. While it is true that an unknown pathogen could give rise to seizures, it seems highly unlikely that a completely unrelated organism would suddenly become active within two minutes of a vaccine. In any event, the respondent's burden to show alternative cause cannot be met by suggesting an idiopathic or unknown cause. *Knudsen*, 35 F.3d at 547-48 (quoting 42 U.S.C. § 300aa-13(a)(2)).

Dr. Shafrir utilized the process of differential diagnosis in reaching his opinion. He stated that when a patient has a severe reaction like what D.P. experienced, within minutes of being injected with an antigen known to cause anaphylaxis, the diagnosis is anaphylactic shock until proven otherwise. He listed breath holding, an underlying condition, and pure chance as other possibilities. As he stated, there was no evidence for breath holding, and while Dr. Bingham suggested that the spitting up of the hash brown in the car on the way to the pediatrician's office may have been the onset of a gastrointestinal illness, the evidence shows that D.P.'s spit up was not due to a gastrointestinal illness, but rather by choking or some similar mechanism. There was no evidence of vomiting gastrointestinal contents. Dr. Patonay, the pediatrician who examined the child before his vaccinations and treated him as he was seizing, noted that the child had no illness at the time of the vaccinations. Pet. Ex. 7 at 21.

While Dr. Bingham testified that, based on his experience, he thought that D.P. suffered an idiopathic seizure, or one without a known cause, he did acknowledge on cross-examination that it was plausible to say that the chances of the child suffering an idiopathic event within two minutes of receipt of a vaccine would be on the order of one in fifty million. Tr. at 140. As demonstrated by Dr. Shafrir's testimony and supporting literature, the likelihood of a biphasic anaphylactic reaction to the vaccines is greater than one in fifty million, and in fact, is more likely than not. Tr. at 137-38; see Pet. Ex. 40 at 64-65.

Although the presentation of seizures without respiratory or cutaneous symptoms is an unusual manifestation of anaphylaxis, it was reasonably demonstrated that such response can and likely did occur in this case. Notably, the child turned blue and was treated with five liters of oxygen, which suggests a possible respiratory problem. Additionally, a physician noted a red rash around the area of the vaccination itself. Pet. Ex. 19 at 178. These findings do suggest a respiratory impairment and hint at a cutaneous symptom. I conclude that petitioner has met her burden under prong two, as Dr. Shafrir presented and applied a reliable methodology in making his differential diagnosis, which is supported by multiple references to the medical literature as cited above.

Additionally, the petitioner has presented adequate evidence that, as Dr. Bingham agreed, what caused the first seizures likely caused the rest. I have concluded that D.P. has suffered from ongoing seizures and cognitive impairments secondary to the brain injury that he suffered during the initial anaphylactic seizure.

iii. *Althen* Prong Three – Temporal Relationship

Prong three of *Althen* requires a showing that the timing of the onset of the anaphylactic response was reasonable. Indeed, Dr. Shafrir found that the timing was not only reasonable but compelling, and that it was helpful in meeting the burden under prong one and two as well. I agree. Anaphylactic reactions generally occur quite rapidly—in minutes to hours from the inciting event. An antigen that is injected is considered to have greater anaphylactic potential than one that otherwise comes in contact with the body. Pet. Ex. 40 at 65. In this case, the child turned blue, went into tonic clonic seizures, and became limp or hypotonic within two minutes of receipt of the vaccines. Pet. Ex. 7 at 17. He was treated with five liters of oxygen which returned him to a baseline pink color, but he remained limp and moaning. Id. at 20. He was sent to the hospital where he appeared fine, but on the way home from the hospital, he had a second seizure about four hours

after the first. Pet. Ex. 18 at 210. This is most consistent with a biphasic anaphylactic reaction as described in the literature. Pet. Ex. 40 at 65. Both experts agreed that vaccines can cause anaphylactic reactions. Tr. at 148.

The timing of the onset of seizures was not only appropriate, but indeed seems compelling in light of the IgE/mast cell mechanism, the absences of alternative reasonable causes, and the rapid onset itself.

E. Alternative Cause

The Vaccine Act permits the respondent to present evidence of an alternative, unrelated cause once the petitioner has made a *prima facie* case sufficient to satisfy the *Althen* prongs. Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. § 13(a)(1)(B); *Knudsen*, 35 F.3d at 548. Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux*, 717 F.3d at 1369. Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition."

The Federal Circuit held that "[s]ection 300aa-13(a)(2)(A) defines unrelated factors as not including 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition.' Since the word 'or' is used with both the adjectives (idiopathic, unexplained, unknown, or hypothetical) and the nouns (cause, factor, injury, illness, or condition), it is apparent that an unrelated factor is not an idiopathic illness, an unexplained illness, or an unknown cause." *Koston v. Sec'y of HHS,* 974 F.2d 157, 160 (Fed. Cir. 1992).

Dr. Bingham proposed that a gastroenteritis, for which he acknowledged there was no direct evidence in this case, was a possible explanation that he favored over an anaphylactic response to the vaccine. Tr. at 122-24. He said that it is common to diagnose a viral illness even though lab reports do not identify a specific organism. Tr. at 161. I find that there was no evidence of a gastrointestinal illness at the time of D.P.'s vaccinations. The post-vaccine vomiting and diarrhea can be explained by the anaphylaxis, as noted in the literature. Kagy and Blaiss state, "the GI tract is also regularly involved (in anaphylaxis). Diarrhea, abdominal cramps, nausea and emesis developed in 25-30% of the patients." Pet. Ex. 40 at 64-65.

In this case, the evidence shows that an anaphylactic reaction to the vaccines administered on August 4, 2008 is much more likely to explain the reaction and seizures D.P. experienced, rather than pure chance or an unknown gastrointestinal illness. The mechanism of anaphylaxis was cogently defined by the testimony and the literature, and the timing was particularly appropriate.

The petitioner's expert, Dr. Shafrir, noted in his expert report that an anaphylactic reaction occurring within four hours of a DTaP or MMR vaccine is a Table injury. He went on to

demonstrate a cause-in-fact injury because the QAI illustration of anaphylaxis did not include the term seizure, but more generally described the most common manifestations of anaphylaxis, including severe respiratory and cutaneous symptoms at times leading to death. In reviewing this aid to interpretation of anaphylaxis, I conclude that the definition provided is illustrative of the condition but not restrictive, as is for example, the definition of a table encephalopathy. The respondent contended that the child did not suffer an anaphylaxis, but for the reasons stated above, I have concluded that Dr. Shafrir has presented persuasive evidence that he did. Accordingly, I find that the petitioner has presented persuasive evidence of a Table anaphylaxis together with sequelae lasting more than six months resulting from the injury caused by the initial anaphylactic event. As the petitioner, in responding to the respondent's contention that the child did not experience an anaphylactic reaction, has presented extensive and persuasive evidence, I find that he has also proved both Table injury Anaphylaxis and a cause-in-fact injury, and is entitled to compensation on either basis.

IV. CONCLUSION

I find that petitioner has presented a persuasive medical theory and a logical explanation of cause and effect in this case, consistent with the theory of causation. The timing of the event was certainly appropriate.

As the Vaccine Injury Table lists anaphylaxis within four hours of the DTaP and MMR vaccinations, and I have concluded that D.P. suffered an anaphylactic reaction two minutes after the vaccines were administered, and that that injury gave rise to ongoing seizures and cognitive delay lasting more than six months, I find that the petitioner has proved his case both as a Table injury and as an off-Table injury by a preponderance of the evidence. I therefore conclude that petitioner presented sufficient evidence to establish causation in this Program and D.P. is entitled to compensation.

A separate damages order will issue.

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master