United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 04-1282V
November 27, 2006
To be Published

JUSTINE ADAMS, a minor, by her parents and natural guardians, STEPHEN and OLIVIA ADAMS,	*	
Petitioners,	*	
v.	*	Entitlement; seizure one day after Prevnar; question of febrile seizure; Dravet's syndrome
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Clifford J. Shoemaker, Renee J. Gentry, Vienna, VA, for petitioners.
Michael A. Milmoe, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

Petitioners filed a petition on August 13, 2004, under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that Justine Adams (hereinafter, "Justine")

[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 clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, petitioner has 14 days to identify and move to delete such information prior to the document's disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access.

suffered seizures that hemophilus B influenza vaccine (HiB), hepatitis B vaccine, and Prevnar vaccine caused in fact. At trial, testimony revolved solely around Prevnar.

A hearing was held on October 13, 2006. Testifying for petitioners were Stephen Adams (Justine's father) and Dr. Carlo Tornatore. Testifying for respondent was Dr. Max Wiznitzer.

FACTS

Justine was born on January 30, 2001. When she was eight months of age, she received HiB, Hepatitis B, and Prevnar vaccines on August 23, 2001. Med. recs. at Ex. 2.

At 4:29 a.m., August 24, 2001, the Escondido Fire Department sent an ambulance which arrived at 4:45 p.m. to Justine's house, leaving at 4:52 a.m. Med. recs. at Ex. 15, p. 2.

On August 24, 2001, at 5:49 a.m., Justine was brought to Palomar Medical Center Emergency Department where Dr. Keri L. London wrote that Justine had signs and symptoms consistent with an acute febrile seizure. Justine did not have meningitis, sepsis, or any other serious disorder, and appeared non-toxic. Justine interacted well with her caregivers. Med. recs. at 172.

Dr. London continued in her records that Justine had received her six-month vaccinations on August 23, 2001 approximately eight hours before the witnessed seizure. Mrs. Adams was sleeping with Justine in bed when she noticed a full-body seizure lasting about one minute. Justine had a short post-ictal state which lasted several minutes, and then was back to baseline. Mrs. Adams noticed some tactile fevers after the immunizations during the course of the prior evening, but did not actually document fever or give Justine antipyretics. Justine ate dinner well without vomiting or diarrhea. She had a normal number of wet diapers. She did not have a rash and had a good activity level. Med. recs. at 177.

On physical examination, Justine had a temperature of 97.6°. She had no difficulty breathing. Justine was alert and active, with good eye contact, and no stridor or drooling. She was playful, smiling, and cooperative with the examiner. Her ears had normal tympani. Her nose was clear and she did not have petechiae. She did have an eczematous rash over her scalp, trunk, upper extremities, and lower extremities, which was her baseline. She had normal muscle tone. Med. recs. at 178.

Also, on August 24, 2001, Justine was brought to her pediatrician Dr. Lauren Burkhart who noted that she had had a seizure on August 23, 2001. Mrs. Adams felt her shaking and she was blue about the lips. She called 911 and Mr. Adams gave Justine a couple of breaths. Justine was staring and had a glazed look. By the time the ambulance arrived, the seizure has stopped. Justine was awake but not herself and was seen at Palomar. The diagnosis there was febrile seizure. The parents stated no fever was documented. Justine slept through the visit and slept until this morning. On examination, all of her signs were normal and she was happy, alert, and playful. Dr. Burkhart's assessment was a seizure. She doubted it was febrile because there was no documentation of an increase in temperature. She questioned whether the seizure was related to Prevnar. Med. recs. at 17.

On October 26, 2001, Justine had an EEG which was normal. Med. recs. at 173.

On November 21, 2001, three months after her first seizure, Justine had another seizure, which lasted seven minutes and was without fever. Med. recs. at 26.

On December 20, 2001, Justine had another seizure while in Texas. This seizure was prolonged and required intubation. For the first time, she was put on anti-convulsants. Med. recs. at 27.

On November 2, 2005, Justine had a neurological/epilepsy consultation with Dr. William W. Sutherling, Medical Director of The Epilepsy and Brain Mapping Program, and Dr. Tatiana Maleeva. Med. recs. at Ex. 16, p. 1. There is a family history of two cousins with febrile convulsions. *Id.* At the age of seven and one-half months, Justine had the onset of her first seizure, which was generalized tonic-clonic, 24 hours after an immunization, when she was in bed asleep, with trembling, shivering, stiffness, apnea, but no tongue biting, lasting about ten minutes. A second similar episode occurred in November with a third episode in December. This third episode lasted about 40 minutes and was one-sided motor activity. It settled down for 10 to 20 minutes and then a seizure began on the other side of Justine's body. *Id.* She required intubation with pharmaceutical coma. Since that time, Justine developed staring spells in 2002. The last time she had a prolonged seizure (45 minutes) was in January 2004, which the parents believe was probably one-sided. *Id.*

Now, Justine has four different seizure types: (1) staring spells for two to thirty seconds, occurring in a cluster of 10 to 15 at a time every morning; (2) right versive tonic seizures where her head and eyes will turn to the right and she goes into a fencer's posture with the right arm extended, with clonic activity in the right hand with the left arm up and behind the head, lasting one to two minutes, occurring three times a week; (3) a left versive seizure, where her left arm extends and she has clonic twitching with her head turned to the left, occurring about once a week; and (4) bilateral stiffening lasting one to two minutes with a generalized tonic seizure, occurring twice a month mostly with overexertion. Med. recs. at Ex. 16, p. 2. Justine has photosensitive staring spells, absences, which can occur due to a ceiling fan, colors on a CRT monitor, or sunlight sparkling on a pool. Justine's seizures have been doubling each year. *Id.*

Her October 26, 2001 EEG was normal, followed by abnormal EEGs in May 2002 and July 2002. Med. recs. at Ex. 16, p. 3. Justine had a vagal nerve stimulator implanted on July 11, 2005 which Mrs. Adams stated helped stop the seizures. *Id.*

The doctors' initial neurological impressions and preliminary working diagnoses included progressive mixed seizure disorder with generalized tonic, partial versive, absence, and photosensitive absence seizures; recurrent status epilepticus; and slight developmental delay since seizure onset but no evidence of progressive encephalopathy over what one would expect for seizures and medication side effects. Med. recs. at Ex. 16, p. 5. They concluded that Justine does not fit into a clear syndrome etiology. Med. recs. at Ex. 16, p. 6. A rare disorder was possible as the family mentioned CNC1A. But there was no definite indication at that time of any progressive metabolic or inborn error or other problems such as this to produce Justine's seizures. *Id.*

Other Submitted Material

Petitioners filed medical articles in Exhibit 12, in support of Dr. Carlo Tornatore's opinion. The first page of the exhibit is an abstract of the first article: "Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine," by R.P. Wise, et al., 292 *JAMA* 14:1702-10 (Oct. 13, 2004). The authors note that there were 4,154 VAERS (Vaccine Adverse Event Reporting System) reports for the first two years of licensure of Prevnar, most frequently for fever, injection site reactions, fussiness, rashes, and urticaria (hives). Immune-mediated events (e.g., anaphylaxis, thrombocytopenia, serum sickness) occurred in one-third of the reports. Seizures were described in 393 reports, including 94 febrile seizures. Med. recs. at Ex. 12, pp. 3-11.

Petitioners filed other articles in this exhibit dealing with either hepatitis B vaccine or HiB vaccine although Dr. Tornatore's testimony focused solely on the Prevnar vaccine that Justine received. The article dealing with hepatitis B vaccine deals with plasma-derived hepatitis B vaccine, which Justine did not receive. She received recombinant hepatitis B vaccine. The article is entitled "Postmarketing Surveillance for Neurologic Adverse Events Reported After Hepatitis B Vaccination. Experience of the First Three Years," by F.E. Shaw, Jr., et al., 127 *Amer J Epidemiology* 2:337-52 (1988). There were five cases of convulsions among 850,000 vaccinees. The authors stated that no conclusive epidemiologic association could be made between any neurologic adverse event and the vaccine. P. Ex. 12, p. 13.

The article on HiB vaccine that petitioners filed is entitled "Effectiveness and Safety of an *Haemophilus influenzae* Type b Conjugate Vaccine (PRP-T) in Young Infants," by C.M. Vadheim, et al., 92 *Pediatrics* 2:272-79 (1993). Out of 10,317 infants, some receiving PRP-T and others receiving recombinant hepatitis B vaccine, reaction rates were higher in PRP-T and included five seizures compared with three seizures in the hepatitis B control group. Three of the seizures occurred within 48 hours of vaccination with PRP-T. The authors could not conclude there was causation because of the small sample size. P. Ex. 12, p. 37.

After hearing testimony from Dr. Wiznitzer about Dravet's Syndrome, the undersigned filed an exhibit(C. Ex. #1) at the hearing as the Vaccine Act permits: 42 U.S.C. § 300aa-12(d)(3)(B)(1) states that a special master "may require such evidence as may be reasonable and necessary." Congress intended for the system

> to allow the proceedings to be conducted in what has come to be known as an "inquisitorial" format, with the master conducting discovery (as needed), cross-examination (as needed), and

> investigation. As was stated in the Report accompanying the original Act, "In order to expedite the proceedings, the power of the special master is intended to replace the usual rules of discovery in civil actions in Federal courts."

Omnibus Budget Reconciliation Act of 1989, Conference Report to accompany H.R. 3299, H.R. Rep. 101-386, at 516, 101st Cong., 1st Sess. (Nov. 21, 1989).

Th article that constitutes C. Ex. #1 is "Dravet's Syndrome (severe myoclonic epilepsy in infancy," by C. Dravet at http://www.ilae-epilepsy.org/ctf/dravet.html. Dr. Dravet describes severe myoclonic epilepsy in infancy (SMEI) in 1978. SMEI begins during the first year of life. Development is normal prior to the onset of seizures. The first seizure type is clonic, often changing sides. The first seizure may be associated with fever. The seizures may recur in 6 to 8 weeks and lead to status epilepticus. Further seizures may be afebrile. Seizure types are tonic-clinic, myoclonic, absence, and complex partial. Psychomotor retardation is usually observed during the second year after the onset of seizures.

After the hearing and as a consequence of Dr. Wiznitzer's testimony about this article, respondent filed "De-Novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study," by S. Berkovic, et al., 5 *Lancet* 488-92 (2006) as Ex. C. The authors determined that in cases of SMEI, there is a genetically determined epileptic encephalopathy that arises de novo, i.e., because of a spontaneous mutation of a gene. In fourteen patients for whom vaccination had been judged the cause of an epileptic encephalopathy, with seizure onset within 72 hours of vaccination, the authors found through molecular genetic analysis, heterozygous mutations of SCN1A in 11 out of the 14 cases. Ex. C. at 489. Eight of the patients had SMEI and four had the related syndrome of SMEB (borderline

SMEI). *Id.* at 490. The authors call mutations in the sodium channel gene SCN1A a well-established finding in SMEI. *Id.* Ninety-five percent of mutations in SMEI occur de novo. The authors state that less than half their patients had documented fever with their first seizure. Neuroimaging data showed no evidence of an inflammatory or destructive process. *Id.* at 491. The authors conclude that "individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunised in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the SCN1A mutation." *Id.*

TESTIMONY

Stephen Adams, Justine's father, testified first for petitioners. Tr. at 4. Although he and his wife had administered Tylenol before Justine's prior vaccinations, they did not administer Tylenol before her August 23, 2001 vaccinations. Tr. at 7, 8. The next morning, at 4:29 a.m., after Justine seized, they called an ambulance, which arrived at 4:45 a.m. Tr. at 12. Justine's seizure lasted longer than a minute. Tr. at 17. However, she did not receive any treatment at the ER. Tr. at 18.

Justine's next seizure was three months later on November 22, 2001. Tr. at 22. The ER notes state that Justine's prior seizure three months earlier was questionably a febrile seizure. Tr. at 25. Mrs. Adams' sister's children have a history of past febrile seizures four times each. *Id.* Justine did not exhibit any change in behavior between her first and second seizures or between her second seizure on November 21, 2001 and her third seizure on December 20, 2001. Tr. at 32-33. Her third seizure lasted one hour. Tr. at 30. On the next day, December 21, 2001, Justine had a 30-minute seizure on the opposite side of the body as the one on December 20,

2001. Tr. at 35. By July 2002, Justine had absence seizures. Tr. at 36. The number of her seizures has doubled year after year. Tr. at 37. At about age three, Justine seemed to lag developmentally. Tr. at 39. She took her first steps and spoke her first words at 10 months. *Id.* and tr. at 40. Dr. William Sutherling noted in 2005 that a rare genetic disorder, SCN1A, was possibly a cause. Tr. at 56.

Dr. Carlo Tornatore, an adult neurologist, testified next for petitioners. Tr. at 59. One percent of his practice consists of child patients in the spasticity clinic. Tr. at 61, 62. His opinion is that Justine's vaccinations, in particular Prevnar, caused Justine's seizures and seizure disorder. Tr. at 64. She had a high white blood count (15.5) on August 24, 2001, which indicates a prolonged convulsion. Tr. at 65. Adrenalin produced during the seizure raised the white blood count. Tr. at 65-66. Moreover, the hemoglobin in her cells was a little bit high and the size of her red blood cells was a little big. Tr. at 66. Although Justine was afebrile in the ER, the ER diagnosed her with a febrile seizure. *Id.* It seemed to be a little seizure. Tr. at 67. But Justine's second seizure three months later was prolonged and tonic-clonic, although not febrile. Tr. at 67, 68.

The vaccines are meant to induce an immune response. Tr. at 69. The vaccines contain a viral protein. Dr. Tornatore testified that an immune response to it crosses the blood-brain barrier and irritates the brain. *Id.* Dr. Sutherling wrote in 1995 that Justine did not have a clear syndrome etiology. Tr. at 71, 73. When the undersigned asked Dr. Tornatore if he wanted the undersigned to focus on all three vaccines or just Prevnar, Dr. Tornatore said that Prevnar is the one where the data is the strongest, but there were data for the other two. Prevnar is pneumococcal vaccine. Tr. at 75. Prevnar is not a viral vaccine because pneumococcus is a

bacterium. *Id.* Dr. Tornatore stated that whether it is a viral protein or bacterial protein is immaterial. Tr. at 76. Once the immune system recognizes it and gets activated, there are other antigens in the brain that may look like those same proteins which form molecular mimicry and they start to attack that particular tissue. *Id.*

Dr. Tornatore explained Justine's further seizures by stating there is kindling in epilepsy, increasing the area of the brain that is irritable. Tr. at 78. When asked if he agrees or disagrees with Dr. Wiznitzer that Justine's not having a fever in the emergency room after her first seizure meant that she did not have fever before the seizure, and it was not a febrile seizure, Dr. Tornatore stated that it was really immaterial whether she had a fever at home or in the ER. Tr. at 81. She was warm. Something was going on with her. *Id.* She was afebrile in the ER but had been warm the night before. What makes sense to Dr. Tornatore is that this was a vaccine-related issue because Justine did not have a high fever. Tr. at 82. The actual physical temperature will cause the seizure, but we know in Justine's case, that did not happen because she did not have fever that was high enough in the ER. But the vaccine caused her to be warm, and that shows she had some response to the vaccination. Because of that response, there was an irritation that caused the seizure. So we do not have to have a fever to cause the seizure because there was an irritation of her brain. Tr. at 83. The peculiarity of Justine's case is that she did not have a fever after having had a prolonged seizure. Tr. at 86. Justine was warm at some point because something happened to her. Tr. at 87.

Dr. Tornatore stated the nervous system is very susceptible to small changes in temperature. Tr. at 90. Justine was acting normally and had no sign of toxic encephalopathy the evening of her vaccinations. Tr. at 90-91. When you start to stimulate the white blood cells, they

make cytokines which cause fever. The cause of seizure was those chemicals that irritated the nerves or maybe the white blood cells themselves attacking the nerves. Tr. at 91.

The undersigned asked Dr. Tornatore if he had heard of Dravet's syndrome, and he responded that he had. *Id.* He does not think Justine had Dravet's syndrome. She did not have monoclonic seizures which are seen in many patients that have it, although there are many patients with Dravet's who do not have monoclonic seizures. Tr. at 92. Most important to Dr. Tornatore is that Dr. Sutherling did not diagnose it and he is an eminent epileptologist who is very well-regarded. *Id.*

The medical article by Wise and others, employed by government agencies, shows that Prevnar is associated with neurologic events in 40 percent of vaccinees. Tr. at 91-94. Prevnar is also associated with fever. Tr. at 94. Both febrile and afebrile seizures have been reported after Prevnar vaccination. Tr. at 96. Justine's cousins had febrile seizures and maybe Justine did not need to have a fever to trigger a seizure; just being warm was enough. Tr. at 99. But Dr. Tornatore admitted that was speculation on his part. *Id.* In the Wise medical article, two patients had seizures on rechallenge with another Prevnar vaccination. Tr. at 100. The authors stated these reports and reports of other illnesses might represent uncommon risks and warranted further assessment. *Id.*

Justine's treating pediatrician Dr. Burkhardt on August 24, 2001 noted "seizure, doubt febrile." Tr. at 102. The doctor also stated "no documented increased temp" and "question, Prevnar-related." *Id.* Justine's being blue about the lips (cyanotic) indicates a prolonged seizure. Tr. at 103. Three-quarters of the seizures following Prevnar in the Wise article were not febrile. Tr. at 106. The vaccines are meant to stimulate the immune system and increase the activity of

the red blood cells which can elevate temperature and directly injure the brain. *Id.* There is a striking temporal relationship between Prevnar and Justine's first seizure. Tr. at 107.

Dr. Tornatore is not board-certified as a pediatric neurologist or as a pediatrician. Tr. at 110. Dr. Tornatore's opinion is not that Prevnar directly invaded Justine's brain. Tr. at 111-12. Of the one percent of his practice involving children, half of that one percent have epilepsy. Tr. at 113. He does not manage the epilepsy. *Id.* He does not consider himself to be an epileptologist. Tr. at 114. Dr. Tornatore is the director of the multiple sclerosis center at Georgetown. Tr. at 115. His testimony is not that Justine had demyelination. *Id.* He has never written a paper on epilepsy. Tr. at 116. He does a fair amount of HIV work. Tr. at 117. Dr. Tornatore is not saying that Justine has an autoimmune disease. Tr. at 121.

On cross-examination, Dr. Tornatore admitted that Justine's case does not involve a fever leading to a seizure. Tr. at 122. She was warm but there was no documentation of a fever. *Id.* The temperature probably rose to a point that it was enough for her to have a seizure. *Id.*

On redirect, Dr. Tornatore stated Prevnar can be and has been associated with seizures. Tr. at 132. There is a logical sequence of cause and effect and a very striking temporal relationship. *Id.* Justine's seizure was within 24 hours of her Prevnar vaccination. *Id.* Half of all the neurologic events listed in the Wise paper occurred within 24 hours of vaccination. *Id.* There is no indication for another cause of Justine's seizures. *Id.*

Dr. Max Wiznitzer, a board-certified pediatric neurologist, testified for respondent. Tr. at 134. He is also a board-certified neurodevelopmental pediatrician and an epileptologist. Tr. at 134, 139. Ninety-five percent of his patients are children. Tr. at 136. Twenty-five to thirty percent of them have epilepsy. Tr. at 138. Dr. Wiznitzer is part of the epilepsy team at his

medical center. Tr. at 139. He has written several commentaries on management of pediatric epilepsy. *Id.*

Dr. Wiznitzer's opinion is that Prevnar did not play a role in causing Justine's first seizure. Tr. at 141. She was vaccinated August 23, 2001 during the day, and was warm at night. Tr. at 142. At 4:29 a.m., her parents called an ambulance which arrived at 4:45 a.m. Presumably, the seizure occurred at around 4:20 a.m. on August 24, 2001. *Id.* Justine was in the hospital ER at 5:03 a.m. At 5:16 a.m., her vital signs included a temperature of 97.6° rectally. Tr. at 143. She had no fever within an hour of her seizure. *Id.* Someone must have a minimum temperature of 101° or 102° to provoke a febrile seizure. Tr. at 144. A temperature of 99° or 100° will not provoke a febrile seizure. *Id.* If a child has a febrile seizure at home and is brought to the hospital, she should still have a fever. *Id.* That is his experience over 20 years of taking care of children. *Id.* He sees children regularly in the hospital with febrile seizures. They always have a fever when they are in the ER. *Id.*

A child who is warm eight hours before the seizure cannot have a febrile seizure eight hours later when she does not have a fever. Tr. at 147. There is new data showing that in animal models and probably in some human, there are certain channels for elements like sodium and calcium in the infant that are temperature-dependent. Tr. at 148. They work fine when there is no fever. Tr. at 148-49. When you get a fever, the fever shuts the channels down and they stop working. That is actually what provokes the febrile seizures. But those channels later on get replaced by more mature systems, which do not shut down in the presence of fever and, hence, there are no febrile seizures. Tr. at 149. The classic febrile seizure population is between six months and three years of age. *Id.* Those children do not have seizures triggered by 99°. Their

seizures would be triggered by temperatures of 101, 102, and 103.° *Id.* If you have a tendency toward the genetic disease Dravet's syndrome, you do not need a temperature as high to provoke a seizure, but it does not matter if the seizure starts at six, seven, eight, or ten months. It will happen because you have Dravet's syndrome. Tr. at 149-50. A seizure does not alter the natural history of Dravet's syndrome. Tr. at 150. Dr. Wiznitzer is not assuming that Justine actually has Dravet's syndrome. *Id.*

If Justine's first seizure had been provoked by fever, Dr. Wiznitzer would have expected that her first seizure would have occurred the evening of the Prevnar vaccination. Tr. at 151. Justine's temperature in the ER after the seizure was 97.6° which is 96.6 orally. Tr. at 152.

Dr. Wiznitzer agreed that if Justine were tactilely warm the evening of her vaccinations, she was reacting to one of her three vaccines. Tr. at 153. Fever can be a reaction to any of the three vaccines. Tr. at 154. Dr. Wiznitzer did not think that Prevnar caused Justine to have an afebrile seizure. Tr. at 155. The data underlying the Wise article came from the Vaccine Adverse Event Reporting System or VAERS. *Id.* This does not mean there is a link between immunization and the event reported. *Id.* VAERS is a surveillance system to see if there are issues going on. Tr. at 156. We cannot take a temporal relationship and assume causality. *Id.* The patients in the Wise article include people who have seizures regularly. *Id.* Most of the individuals received Prevnar together with another vaccine. Most of them got acellular DPT which can cause febrile seizures if they get a fever. Tr. at 157. None of the data of who was febrile and afebrile and who received Prevnar alone is given in the article. Tr. at 157-58. The Wise article was written in 2003 and no one has come along subsequently to say there is definite proof that Prevnar causes idiopathic epilepsy. Tr. at 161.

Dr. Wiznitzer stated there is insufficient data whether or not Justine has Dravet's syndrome. *Id.* It is also known as severe myoclonic epilepsy in infancy as well as polymorphic epilepsy in infancy. Tr. at 161-62. Dr. Wiznitzer has patients with Dravet's syndrome. Tr. at 162. Few of them ever had monoclonic seizures. *Id.* Dr. Dravet said the child does not need to have a monoclonic seizure in order to have the syndrome. Tr. at 163.

The natural history of Dravet's syndrome is that the child usually in the first year of life will have a prolonged seizure which can occur on either or both sides of the body. *Id.* Many times, fever may provoke the first seizure. *Id.* When the seizure involves one side of the body, it then changes sides. *Id.* The child gets clonic, either hemiclonic or generalized clonic, seizures. The child shakes all over or just on one side. As time goes on, the child develops seizures of different types. Tr. at 164. The child can have monoclonic seizures which are often photosensitive. A third type of seizure is absence or staring seizures which are slow in duration. A fourth type of seizure is complex partial seizures arising from one side of the brain. *Id.* They make the child turn her head and posture. There can be automatisms, mouth movements, such as sucking and licking, and moving the hands in funny patterns. Tr. at 165. The first few EEGs are fine. Only as time passes does the EEG start to show the epileptic form of activity. *Id.* First the EEG shows discharges occurring focally or multifocally coming from various parts of the brain. Then, you have an EEG showing generalized discharges in the background. *Id.*

Developmentally, children with Dravet's syndrome seem to be all right for the first few years. Then they show a slow or stagnational development. *Id.* In addition, there is a slowing of head growth. The child starts with a normal head size but then it drops in percentile. Tr. at 166.

Many of the children with Dravet's syndrome also have episodically unexplained weakness on one side of the body. They have seizures in their sleep. Some have autism. *Id.*

Dr. Wiznitzer had a strong sense that Justine should be checked for Dravet's syndrome. Tr. at 166. When you look at her history, she started with seizures that were generally clonic, shaking all over, or one-sided shaking, full-blown in nature, and some provoked by fever. Tr. at 166-67. She had adequate development for a period of time. Then she started developing other seizure types, absence and versive seizures. She had an evolution of an EEG pattern which is consistent with Dravet's syndrome. Initially, the EEG was normal and then it started showing discharges that were generalized and focal, depicting a gradual slide from background to present. Tr. at 167.

Developmentally, Justine was adequate early on and then stagnated by the age of three years. *Id.* Justine had a slowing of head growth. She started at the 75th percentile for the first six months of life. At nine and 10 months, she was at the 50th percentile. At 19 months, she went below the 50th percentile between the 25th and the 50th. At a little over three years of age, her head circumferences was at the 25th percentile. Tr. at 167-68. Justine's gradual slowing of head growth is commensurate with a Dravet-type of epilepsy. It is not something he sees in his patients who have for example epilepsies associated with prior provocation, such as trauma or hypoxic-ischemic injury. For those children, their head circumference is what it is irrespective of how many seizures they have. Tr. at 168. Justine's decreasing head size is indicative of her condition. *Id.* It is possible that Justine has Dravet's syndrome. *Id.*

He would recommend that Justine's parents test her for the SCNA1 gene. Tr. at 169. The majority of children with Dravet's syndrome test positive for it. *Id.* The fact that Justine has

not been tested for the SCNA1 gene prevents Dr. Wiznitzer from diagnosing her with Dravet's syndrome. Tr. at 170. Clinically, Justine fits the profile or criteria of Dravet's syndrome. *Id.* If Justine were diagnosed with Dravet's syndrome, the type of medications she receives should be better than what she is receiving. Tr. at 171. The SCNA1 is a sodium gene. The gene mentioned by Dr. Sutherling was a calcium gene. Tr. at 172. The problem with the SCNA1 gene in Dravet's syndrome is that there is a mutation of it. Tr. at 175. As a consequence, the sodium channel does not work on it. *Id.*

A fever that happens eight hours before a seizure and goes away is not a contributor to a seizure. Tr. at 176. A fever at seven or eight months does not alter the natural history of Dravet's syndrome. Tr. at 177. With Dravet's syndrome, you have a genetic mutation due to truncation and it is a spontaneous mutation. *Id.* With Dravet's syndrome, it does not matter when the seizure starts. The illness has the same natural history. Tr. at 178. The child follows the same kind of course, the same number of seizures, the same impairment to development, the same impairment to head growth, and the same EEG pattern. *Id.*

If Dr. Tornatore's theory of an immune-mediated injury to the brain were correct, it would not explain why Justine's initial EEG was normal but, years later, she would have multiple areas of abnormality on EEG. Tr. at 181. One does not get kindling in the brain after one seizure. *Id.* One does not get kindling after two seizures. *Id.* You do not get kindling after three seizures. *Id.* Kindling shows up in the mouse model which involves major controversy as to whether it is fully applicable to humans. Tr. at 181-82. In the short time frame here, kindling would not be applicable to Justine. Tr. at 182.

The underlying condition is provoking Justine's seizures and causing her developmental delay. Tr. at 183. When one has many seizures, one can develop an epileptic encephalopathy, a clouding of the brain, that also causes stagnant development. *Id.*

If Justine had an immune injury to her brain from Prevnar, she should have had multiple areas of her brain injured by the immune system and an encephalopathy. She should have had persistent impairment. But she did not have encephalopathy. Tr. at 184. After her postictal state, Justine went back to normal behavior. Tr. at 185. It is not biologically plausible that she had an immune-mediated injury. *Id.* Dr. Tornatore testified that it is the pneumococcal protein that provokes the antigenic response, but the package insert for Prevnar states that it is the pneumococcal sugars (polysaccharide) that provoke the antigenic response. *Id.* Dr. Wiznitzer has never heard that a polysaccharide reaction causes this type of brain injury. *Id.* As for the Wise article's listing an acute disseminated encephalopmyelitis (ADEM) occurring 12 hours after Prevnar vaccination, Dr. Wiznitzer stated that is awfully fast for getting ADEM after a vaccination. Tr. at 186. He would not say there was a causal relationship to Prevnar vaccine. *Id.*

Dr. Wiznitzer took issue with Dr. Tornatore's statement that Justine's being blue about the lips after her first seizure meant that her first seizure was prolonged. Tr. at 190. The reason the lips turn blue and the face turns pale is that the body is channeling blood to important areas of the body because the body interprets the seizure as a stressor. This is a fight or flight response. Tr. at 192. Lips can turn blue during a seizure that lasts only 30 seconds. Tr. at 194. There is no data to support the idea that a seizure for longer than seven minutes causes brain damage. Tr. at 193. If that were true, you would have damage to other organs first because the fight or flight

response protects the brain. Tr. at 194. Justine's medical records do not show that she had damage to her kidneys or liver after her first, second, third or fourth seizure. *Id.*

Justine's pediatrician's concern about her milestones and motor development would fit the diagnosis of Dravet's. Tr. at 195. As for Dr. Tornatore's testimony that the rise of Justine's white blood cell count indicated a prolonged seizure, Dr. Wiznitzer said that the white blood count elevation just implies that the body has been stressed. It does not tell you how long the stress has been going on. However, Dr. Wiznitzer agrees that the first seizure was probably 11 minutes long. *Id.*

Dr. Wiznitzer was very interested that, from the very beginning, Justine had an elevated mean corpuscular volume, i.e., her red blood cells were bigger than normal. This was before she received medication. Tr. at 196. Every time she had a complete blood count, the numbers rose and went to 100 and over. One was even 107. Dr. Wiznitzer recommended that Mr. Adams see if that reflected something pertaining to vitamins. He does not know if that is related to her seizures. This excessive number came up no matter which laboratory was doing the analysis. *Id.*

Dr. Wiznitzer emphasized that the Wise article was not establishing a cause and effect relationship. The authors of the Wise article had all the data, which we as readers do not. Therefore, a reader cannot conclude more than the authors did about causation. Tr. at 197-98. As for the Shaw article concerning hepatitis B vaccine, it discussed the vaccine that is no longer administered which is a yeast vaccine from a different source. One cannot extrapolate potential adverse reactions from one type of vaccine to another. Tr. at 198. Moreover, the hepatitis B vaccine article petitioners filed concerned adults. The authors did not find any relationship to seizures. The number of seizures they found in the vaccinated population was lower than

baseline. *Id.* The article about pneumococcus influenza type B did not have a large enough group. They had two seizures without fever, which did not differ from the control group. The conjugate used was tetanus. But the conjugate used in Justine's case was pneumococcus-derived. Tr. at 199.

On cross-examination, Dr. Wiznitzer admitted that Justine had never been diagnosed with Dravet's syndrome. *Id.* In the Wise article, even when we know that only Prevnar was administered and not in combination with other vaccines, we do not know the age of the vaccinees. Tr. at 202. Temperature can trigger a seizure but not alter the natural history of Dravet's syndrome. Tr. at 206. Those with Dravet's are going to develop these seizures anyway. They were going to have the same seizure pattern anyway. They were going to have the same time sequence, the same developmental issues, and the same effects anyway whether they seized at four, six, or nine months. *Id.* Justine's having three months before her second seizure, then one month until her next seizures, then another month until many seizures is the Dravet's pattern. *Id.* Severe catastrophic epilepsies of infancy start because a child is going to have it. It does not matter if it starts a month earlier or later. Tr. at 208. If Prevnar caused Justine's first seizure and she has Dravet's syndrome, Prevnar just brought out a tendency that was already there. *Id.*

Dr. Wiznitzer stated that Dr. Tornatore's testimony has no real science to support it. It is really speculation. Tr. at 212. Dr. Wiznitzer stated he has offered a true differential diagnosis and it is up to Justine's parents if they want to pursue it. *Id.* Mr. Adams in his testimony stated that one of the doctors caring for Justine at the Children's Hospital in San Diego raised the question of Dravet's. Tr. at 213. Mr. Adams, on questioning, reiterated that this was so. It was the neurologist on call, Dr. Nespeca, at Children's Hospital who got a history from Justine's

parents and asked about Dravet's. Subsequently, the Adamses discussed Dravet's with their regular neurologist Dr. Trauner and talked about getting the genetic test, but the doctor did not push them in that direction. Tr. at 216-17.

Dr. Wiznitzer stated that Justine clearly fits the Dravet's syndrome profile. In the old days, before genetic testing, he always told a family with a child who had this clinical picture that the diagnosis most clearly fit Dravet's syndrome. *Id.* Dr. Wiznitzer testified that, clinically, it is more likely than not that Justine has Dravet's syndrome. She has not been tested for the gene but not all children are positive for the gene who have Dravet's. Tr. at 214, 215. Dr. Dravet states in her article that the child does not have to have myoclonus to have the syndrome. Tr. at 217. Even if Justine had the genetic test and the result were negative, Dr. Wiznitzer's opinion is that Justine still has Dravet's syndrome because she fits the clinical profile. Tr. at 218. If the genetic test were negative, it just means we do not know what other gene is involved here. *Id.* Dr. Wiznitzer's testimony is that Justine more likely than not has Dravet's syndrome because she clearly fits the profile of the syndrome clinically. Tr. at 219. No doctor has diagnosed Justine with Dravet's. Tr. at 220.

DISCUSSION

To satisfy their burden of proving causation in fact, petitioners must offer "(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. Secretary of HHS, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of HHS, 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[.]"

In Capizzano v. Secretary of HHS, 440 F.3d 1317, 1325 (Fed. Cir. 2006), the Federal Circuit said "we conclude that requiring either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in Althen...."

Close calls are to be resolved in favor of petitioners. Capizzano, supra, at 1327; Althen, supra, at 1280. *See generally*, Knudsen v. Secretary of HHS, 35 F.3d 543, 551 (Fed. Cir. 1994).

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, supra, at 1149. Mere temporal association is not sufficient to prove causation in fact. Hasler v. US, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984).

Petitioners must show not only that but for Prevnar, Justine would not have had a seizure disorder, but also that Prevnar was a substantial factor in bringing about her seizure disorder. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, supra, 418 F.3d at 1278; Grant, supra, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, supra, 35 F.3d at 548-49). To the undersigned, medical probability means biologic credibility or plausibility rather than exact biologic mechanism. As the Federal Circuit stated in Knudsen:

> Furthermore, to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program. The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal "compensation program" under which awards are to be "made to vaccine-injured persons quickly, easily, and with certainty and generosity." House Report 99-908, *supra*, at 3, 1986 U.S.C.C.A.N. at 6344.
>
> The Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.

35 F.3d at 549.

The Federal Circuit stated in Althen, supra, at 1280, that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."

The Federal Circuit in Capizzano emphasized the opinions of petitioner's four treating doctors in that case. 440 F.3d at 1326.

In the instant action, both medical experts acknowledged that Justine's tactile warmth the evening of her vaccinations was due to her vaccinations. From there, the testimony diverged. The undersigned can find it probable that Justine's temperature the evening of her vaccinations was not very high or her parents, who impressed the undersigned as conscientious and observant, would have administered baby Tylenol to Justine. Mr. Adams testified that they administered Tylenol to Justine before all of her previous vaccinations. The fact that they did not do so after the August 23, 2001 vaccinations suggests that her temperature was not particularly high.

A second reason to believe that Justine's temperature the evening of her vaccinations was not high is that her parents did not take her temperature. If it had been high, these attentive parents would have been concerned enough to take it and monitor it.

A third reason to believe that Justine's temperature the evening of her vaccinations was not high was that, as they told the ER the next morning, her behavior the evening before was totally normal. She ate normally, used the usual number of diapers (which were wet), and had a good activity level. They never mentioned any difficulties with Justine's going to sleep or crying excessively, which means that she behaved appropriately.

The first issue is whether or not Justine's seizure the next morning at 4:00 a.m., eight hours after her tactile warmth, was febrile. Certainly, the undersigned accepts in light of the Wise article and both medical experts' testimony that Prevnar can cause fever. The undersigned is also cognizant that the ER diagnosed Justine as having a febrile seizure. But her pediatrician Dr. Burkhart questioned this. As far as a Capizzano emphasis on what the treaters' opinion is, Dr. Burkhart's questioning the ER's diagnosis of febrile seizure cancels out in the diagnosis in terms of what the medical records show. The undersigned then looks at the experts' testimony.

Dr. Tornatore based his opinion that Justine had a febrile seizure on the ER diagnosis, ignoring Dr. Burkhart's questioning that diagnosis. However, Dr. Tornatore later retracted his opinion and opined instead that the Prevnar vaccine did something to cause Justine's warmth and that something irritated her brain so that when her temperature returned to normal the morning of her seizure, it was still the effect of Prevnar vaccine on Justine's brain that caused her seizure.

Respondent's expert, Dr. Wiznitzer stated that Justine could not have had a febrile seizure at 4:20 a.m. and yet entered the ER within the hour with a normal temperature of 97.6° rectally. It would take a temperature of 101° or 102° to prompt a febrile seizure. He explained that Justine had Dravet's syndrome, a type of epilepsy that begins in a child usually in his or her first year with unexplained seizures that eventually take numerous forms and proceed to

psychomotor retardation and decreasing head size. Often, this type of epilepsy comes from a spontaneous mutation of a gene (SCN1A). Justine's clinical picture is an exact profile of Dravet's syndrome: the beginning seizure followed by normal behavior and an interlude of time before the next seizure; the gradual diminution of head size, the gradual loss of motor milestones; the seizure type varying and also manifesting one side and switching to the other side of the body.

(Dr. Wiznitzer began his testimony stating that Dravet's was only a possibility here because Justine had not taken the appropriate genetic test to determine if she had the spontaneous mutation underlying Dravet's syndrome. But as he continued testifying, Dr. Wiznitzer believed that Justine probably has Dravet's based on her fitting the Dravet's clinical profile and, if she ever took the genetic test and it turned out negative, not all children test positively for a particular Dravet's gene because there is more than one gene that underlies the syndrome.)

Dr. Tornatore's opinion on causation at first rested solely on Prevnar's causing Justine to have a febrile seizure. He stated that Prevnar contains a viral protein (later recognizing that it would be a bacterial protein since Prevnar is not a viral vaccine) and that an immune response to it crossed Justine's blood-brain barrier. Later, he admitted that Justine's seizure was probably afebrile but it did not matter to him because Prevnar, by causing warmth the evening before, had irritated Justine's brain, causing a seizure eight hours later.

Dr. Tornatore's practice is overwhelmingly that of adult neurology with an emphasis on multiple sclerosis. Dr. Wiznitzer, on the other hand, deals overwhelmingly with children with neurologic conditions, principally epilepsy about which he has written. He is not only a board-certified pediatric neurologist, but also a board-certified neurodevelopmental pediatrician and

epileptologist. Dr. Wiznitzer's experience vastly outweighs Dr. Tornatore's in the area of childhood epilepsy.

Dr. Wiznitzer stated that someone such as Justine with Dravet's syndrome will have her pattern of seizures regardless of when the onset is. Thus, even if Prevnar, for some unknown reason could have triggered her first seizure, Justine would have had Dravet's syndrome with its repetitive seizures, gradual developmental delay, and reduction in head size, regardless of when she seized. As the article he furnished after trial supports, there is a timing element in epilepsy which explains the occurrence of symptoms.

Comparing the two doctors and their testimonies, the undersigned is persuaded by Dr. Wiznitzer's expertise and knowledge as a practicing pediatric neurologist, neurodevelopmental pediatrician, and epileptologist. The Wise article that Dr. Tornatore relied upon extensively to support his opinion itself does not posit causation. It is based on passive reporting to VAERS. Even though there are reports of afebrile seizures following Prevnar vaccination, the authors conclude that there should be further investigation. They do not provide data to conclude that these seizures are causally related to Prevnar. The undersigned can conclude no more than the authors, who are familiar with their data, conclude.

Dr. Tornatore's theory of Prevnar crossing the blood-brain barrier seems barren of support in light of the fact that Justine's behavior remained normal when she was warm to the touch the evening of the vaccinations. She ate normally, used the normal number of diapers, and had a good activity level. Dr. Tornatore's medical theory does not seem plausible nor does he present a logical sequence of cause and effect because one would expect that if Prevnar irritated Justine's brain on the evening of her vaccination, she would not have eaten normally, had the

usual number of wet diapers, and had a good activity level. As Dr. Wiznitzer pointed out, if Justine were having a reaction to Prevnar such that it was going to cause a seizure, the vaccine should have caused the seizure the evening of the vaccination, but it did not. To posit that there was brain irritation in the absence of any abnormal behavior is speculation on Dr. Tornatore's part. Therefore, the undersigned does not accept his medical theory of an irritation of Justine's brain as plausible.

Dr. Tornatore made a number of other statements in his testimony that do not add to his credibility. He stated that Justine's blue lips meant that her first seizure was prolonged whereas Dr. Wiznitzer explained blue lips merely indicate that the body is in fight or flight posture, not the length of a seizure. Dr. Tornatore stated that pneumococcal protein in Prevnar caused the reaction in Justine's brain so as to prompt her first seizure whereas Dr. Wiznitzer stated that pneumococcal sugars (polysaccharides) in the vaccine, not pneumococcal protein, cause antigens to form and this information is in the Prevnar package insert. Dr. Tornatore stated that Justine's elevated white count showed that she had a prolonged first seizure whereas Dr. Wiznitzer stated that an elevated white count merely shows the body is being stressed, not the length of the seizure. Dr. Wiznitzer commented on the unusual shape of Justine's red blood cells which Dr. Tornatore never detected or testified about. Dr. Tornatore explained Justine's gradual decline by the theory of kindling whereas Dr. Wiznitzer stated kindling as applied to the mouse model is very controversial, that the facts in Justine's case do not support the theory of kindling, and it is unknown if kindling applies to humans. Time and again, Dr. Wiznitzer seemed the more knowledgeable and credible of the two experts.

Dr. Tornatore's testimony does not provide a logical sequence of cause and effect because he assumes that there is no other underlying reason for Justine's seizure disorder except for Prevnar vaccine. In light of Dr. Wiznitzer's persuasive testimony that she has Dravet's syndrome based on her clinical picture, Dravet's is a plausible, alternate explanation for why Justine has her seizure disorder.

As for the third Althen criterion of medically appropriate time frame, 24 hours seems to fulfill the criterion. But the Federal Circuit in Shyface also requires petitioners to prove that but for the vaccine, Justine would not have had her seizure disorder. Here, Dr. Wiznitzer testified that even if Prevnar had for some reason triggered Justine's first seizure, she would have had Dravet's syndrome in any event, with its classic pattern of infrequent seizures, normal behavior, more frequent seizures, different types of seizures, gradually declining head size, and gradual developmental delay. There is a genetic basis to Dravet's syndrome consisting of a spontaneous mutation. Like a clock, the mutated gene controls the timing of the occurrence of the syndrome. Prevnar vaccine does not cause Dravet's syndrome. A spontaneous mutation of a gene causes it. Therefore, the medically appropriate time frame is irrelevant in light of the fact that petitioners cannot prove that, but for Prevnar vaccine, Justine would not have had her seizure disorder.

The Berkovic article that respondent filed after the hearing which Dr. Wiznitzer discussed during the hearing deals with SMEI (also known as Dravet's syndrome). The authors state that individuals with mutations leading to SMEI or borderline SMEI (SMEB) seem to develop SMEI or SMEB whether or not they are vaccinated in their first year of life. The authors did not think that avoiding vaccination, as a potential trigger for a seizure, would prevent onset of "this devastating disorder in patients who already harbour the SCN1A mutation."

Without satisfactory proof of the first two of the three criteria of Althen, i.e, plausible medical theory and logical sequence of cause and effect, and the irrelevance of the third criterion (medically appropriate time frame between vaccination and injury) because Justine would have had Dravet's in any event, petitioners have failed to prove a prima facie case of causation in fact.

Because of Dr. Wiznitzer's far superior knowledge compared with Dr. Tornatore of childhood epilepsy and Dravet's syndrome, and his understanding of what is and is not a febrile seizure, the undersigned views his testimony as more credible that Dr. Tornatore's. Medical literature, in the form of the Berkovic article, supports Dr. Wiznitzer's opinion that Justine's seizures would have occurred with or without vaccination and she would still have the devastating epileptic form called SMEI or Dravet's syndrome which afflicts her.

Petitioners have not proved that but for Prevnar vaccine, Justine would not have SMEI. Petitioners have also not proved that Prevnar was a substantial factor in causing her SMEI. Petitioners have not proved a prima facie case of causation.

CONCLUSION

This petition must be 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 in accordance herewith.[2]

IT IS SO ORDERED.

November 27, 2006
DATE

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

[2] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party's filing a notice renouncing the right to seek review.