In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 26, 2021

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STACY GINN and JENNIFER GINN, Parents of R.G., a minor,	*	PUBLISHED
	*	No. 16-1466V
Petitioners,	*	
	*	Special Master Nora Beth Dorsey
v.	*	
	*	Entitlement; Diphtheria-Tetanus-Acellular-Pertussis ("DTaP") Vaccine; Inactivated Polio ("IPV") Vaccine; Haemophilus Influenzae Type B ("Hib") Vaccine; Measles-Mumps-Rubella ("MMR") Vaccine; Influenza ("Flu") Vaccine; Febrile Seizures; Epilepsy.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	
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Ronald C. Homer, Conway, Homer, P.C., Boston, MA, for petitioners.
Terrence K. Mangan, U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

I. INTRODUCTION

On November 7, 2016, Stacy Ginn and Jennifer Ginn ("petitioners"), on behalf of their minor child, R.G., filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2012).[2] Petitioners alleged that as a result of receiving a diphtheria-tetanus-acellular-pertussis ("DTaP"), inactivated polio ("IPV"), haemophilus influenzae type b ("Hib"), measles-mumps-rubella ("MMR"), and

[1] Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

influenza ("flu") vaccines on November 15, 2013, R.G. suffered a neurological injury, specifically epilepsy. Petition at 1 (ECF No. 1). Respondent argued against compensation, stating that "petitioners have not provided preponderant evidence in support of their petition." Respondent's Report ("Resp. Rept."), filed May 24, 2017, at 7 (ECF No. 19).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that petitioners have provided preponderant evidence that the vaccines that R.G. received on November 15, 2013, triggered a febrile seizure which caused or contributed to the development of a seizure disorder and epilepsy, which satisfies their burden of proof under Althen v. Secretary of Health and Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, petitioners are entitled to compensation.

II. BACKGROUND

A. Summary of Relevant Facts

The facts have been covered in the parties' pre- and post-hearing submissions and the expert reports, and will not be repeated here in detail.[3] A very brief chronology is helpful for context.

R.G. was born on November 11, 2009, and was healthy prior to the vaccinations at issue. At his four-year-old well child visit on November 15, 2013, he received MMR, DTaP, IPV, Hib, and flu vaccinations. Petitioners' Exhibit ("Pet. Ex.") 1 at 1. Later that night R.G.'s parents heard a strange noise and found R.G. shaking, unresponsive, and not breathing. Pet. Ex. 10 at 2. His lips were blue. Id. They called 911, and R.G. was transported by ambulance to the hospital. Id. He was seen by a physician in the emergency department ("ED") who noted that R.G. likely had a febrile seizure. Pet. Ex. 7 at 5. The ED physician noted that R.G. had received vaccinations less than 24 hours before the seizure. Id. at 4-5.

On January 23, 2014, R.G. had a second seizure. Pet. Ex. 7 at 23. Again, he was seen in the ED, where the physician noted that he had a seizure two months before, thought to be related to fever and/or vaccinations. Id. R.G. was referred for an electroencephalogram ("EEG"). Id. at 24.

R.G. had the EEG on January 29, 2014. Pet. Ex. 5 at 389. The EEG was abnormal. Id. It showed an "independent foci of spike activity in the right parieto posterior temporal occipital and left occipital regions." Id. The findings "indicate[d] the presence of a focal potentially epileptogenic process in these regions." Id. at 389-90.

Subsequently, on February 25, 2014, R.G. saw pediatric neurologist, Dr. Wilfred Castro-Reyes, who noted that R.G.'s first seizure occurred in November with fever after receiving

[3] See Petitioners' ("Pet.") Pre-Hearing Brief ("Br."), filed July 21, 2020 (ECF No. 81); Resp. Pre-Hearing Br., filed Aug. 20, 2020 (ECF No. 100); Pet. Post-Hearing Br., filed Nov. 30, 2020 (ECF No. 106); Resp. Post-Hearing Br., filed Jan. 4, 2021 (ECF No. 111).

vaccinations. Pet. Ex. 5 at 418. Dr. Castro-Reyes diagnosed R.G. with "[e]pilepsy with an abnormal EEG that showed multifocal spikes." Id. at 419. She prescribed anticonvulsant therapy, Trileptal. Id.

Since then, R.G. has had more seizures and he continues to see his neurologist every six months and remains on medication for treatment of his epilepsy. See generally Pet. Ex. 5. His current neurologist, Dr. Garrett Burris, has opined that R.G. will require medication and neurological follow-up until the age of twenty-two. Id.

B. Febrile Seizures and Epilepsy

Febrile seizures occur in 2-5% of children under the age of five. Resp. Ex. E at 3.[4] A febrile seizure is defined as "an epileptic seizure . . . occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the [central nervous system]." Resp. Ex. D at 3.[5] "In the past, it was believed that most febrile seizures represented a form of epilepsy and that the prognosis was not favorable," but over the last several decades, and with the benefit of more research and data, "[t]he prognosis for febrile seizures usually has been found to be good." Resp. Ex. E at 3.

There are two types of febrile seizures: simple and complex. Resp. Ex. E at 3. A febrile seizure is complex, "if it is focal, prolonged (lasting more than either 10 . . . or 15 minutes), or multiple." Id. Most febrile seizures are simple, and only approximately 20-30% are complex. Id. A complex seizure is defined as a focal seizure, one or more seizures occurring within 24 hours, or a seizure lasting longer than 15 minutes. Transcript ("Tr.") 72. The causes of febrile seizures are multifactorial and include inflammation, brain pH, and genetic factors. See generally Resp. Ex. M.[6]

Epilepsy is defined as two or more seizures, "unprovoked by any immediate identified case." Resp. Ex. D at 3. Evidence shows febrile seizures are associated with an increased risk of subsequent epilepsy, and that epilepsy develops in 2-4% of children with a history of febrile seizures. Resp. Ex. F at 2.[7] The risk for development of epilepsy after a simple febrile seizure is two times higher than the general population, and for a complex febrile seizure, the risk is higher. Tr. 22. If a "febrile seizure is focal, that makes it complex. And the risk of subsequent epilepsy is higher. It's 5 to 10 percent." Tr. 123.

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[4] Shlomo Shinnar, Febrile Seizures, in 1 Swaiman's Pediatric Neurology: Principles and Practice, 790 (Kenneth F. Swaiman et al. eds., 5th ed. 2018).

[5] Comm'n on Epidemiology & Prognosis, Int'l League Against Epilepsy, Guidelines for Epidemiologic Studies on Epilepsy, 34 Epilepsia 592 (1993).

[6] S. Gatti et al., Mechanisms of Fever and Febrile Seizures: Putative Role of the Interleukin-1 System, in Febrile Seizures, 169 (Tallie Z. Baram & Shlomo Shinnar eds., 2002).

[7] Anne T. Berg et al., A Prospective Study of Recurrent Febrile Seizures, 327 New Eng. J. Med. 1122 (1992).

"There seems to be a consensus that seizures affect brain function." Pet. Ex. 13, Tab HH at 7.[8] "The vulnerability of the brain to seizure-induced injury is age-specific . . . . Experimental studies show that immature brains are highly prone to develop seizures . . . but are more resistant to seizure . . . induced damage than adult brains." Id. at 8. Recent animal data suggest that seizures "may produce age-specific changes that are not confined to cell loss." Id. "Structural, functional, and neurochemical changes have been reported after brief and prolonged seizures in human beings. However, the significance of these changes is unclear." Id.

Epileptogenesis "refers to [the] process in which an initial brain damaging insult triggers a cascade of molecular and cellular changes that eventually lead to the occurrence of spontaneous seizures." Pet. Ex. 13, Tab TT at 1.[9] In other words, "epileptogenesis is a process determined by conversion of the healthy brain into the epileptic brain. In epileptic seizure development . . . abnormal and excessive electronic discharges" occur. Pet. Ex. 13, Tab E at 3.[10] The immune system is suggested to play a role in seizure development. Id.

C. Experts Qualifications

Both experts are well qualified to opine on the causation issues presented by the facts and circumstances presented in this case.

1. Petitioners – Dr. Mahbubul Huq

Dr. Huq is a clinical geneticist and a board certified pediatric neurologist at Children's Hospital of Michigan. Pet. Ex. 13 at 1. He completed pediatrics and neurology residencies at Wayne State University, as well as clinical and postdoctoral fellowships in genetics at Baylor College of Medicine and the University of British Columbia. Pet. Ex. 14 at 1. Dr. Huq is a Professor of Pediatrics and Neurology at Wayne State University in the "Clinician Educator track." Pet. Ex. 13 at 1. He has an active clinical practice and has authored or co-authored over 75 publications including published peer reviewed articles on the genetics of epilepsy and neurodevelopmental disorders. Id.; Pet. Ex. 14 at 14-21.

2. Respondent – Dr. Shlomo Shinnar

Dr. Shinnar is board certified in Pediatrics and Neurology with an added Qualification in Epilepsy. Resp. Ex. A at 2. He completed residencies in Pediatrics and Neurology at Johns Hopkins Hospital. Id. Dr. Shinnar is a Professor of Neurology, Pediatrics and Epidemiology,

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[8] Sheryl R. Haut et al., Susceptibility of Immature and Adult Brains to Seizure Effects, 3 Lancet Neurology 608 (2004).

[9] Asla Pitkanen A & Katarzyna Lukasiuk, Molecular and Cellular Basis of Epileptogenesis in Symptomatic Epilepsy, 14 Epilepsy & Behavior 16 (2009).

[10] Feyza Alyu & Miriş Dikmen, Inflammatory Aspects of Epileptogenesis: Contribution of Molecular Inflammatory Mechanisms, 29 Acta Neuropsychiatrica 1 (2017).

and Population Health, and the Hyman Climenko Professor of Neuroscience Research and the Director of the Comprehensive Epilepsy Management Center at Montefiore Medical Center and the Albert Einstein College of Medicine. Resp. Ex. A at 2. He has authored or co-authored more than 200 publications, a majority which relate to seizure disorders. Id.

III. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 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 Health & Hum. Servs., 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).

Petitioners burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires petitioners to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioners must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

B. Causation

To receive compensation through the Program, petitioners must prove either (1) that R.G. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that R.G. suffered an injury that was actually caused by a vaccination. See §§ 13(a)(1)(A), 11(c)(1); Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Because petitioners do not allege that R.G. suffered a Table Injury, they must prove that the vaccinations R.G. received caused his injury. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccines and R.G.'s injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccines were the reason for R.G.'s injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and R.G.'s injury ("Althen Prong Three"). § 13(a)(1); Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioners must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Boatmon v.

Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359 (Fed. Cir. 2019); see also Knudsen v. Sec'y of Health & Hum Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on their assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether petitioners are entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in petitioners' favor when the evidence weighs in their favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in petitioners' favor).

C. Diagnosis

As Federal Circuit precedent establishes, in certain cases it is appropriate to determine the nature of an injury before engaging in the Althen analysis. Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010). Since "each prong of the Althen test is decided relative to the injury[,]" determining facts relating to the claimed injury can be significant in a case like this, where R.G. has an evolving course of symptoms, resulting in a diagnosis of epilepsy. Id. Thus, before determining if petitioners have met each prong of Althen, the undersigned addresses whether they have established, by a preponderance of the evidence, that R.G. suffered from epilepsy.

Prior to the hearing, there was a question as to whether R.G. had epilepsy. Petitioners' expert, Dr. Huq, opined that R.G. did have epilepsy; however, respondent's expert, Dr. Shinnar, did not agree. Instead, Dr. Shinnar opined that R.G. had a mild seizure disorder. At the hearing however, after Dr. Shinnar had the opportunity to review R.G.'s medical records from August 10, 2018, he agreed that R.G. does have epilepsy. Tr. 101. Dr. Shinnar changed his opinion based on the August 2018 records that showed that R.G. had an unprovoked seizure.

However, Dr. Shinnar disagreed that R.G.'s diagnosis of epilepsy was appropriate before 2018. He disagreed with the diagnosis of epilepsy made by R.G.'s treating physician, Dr. Castro-Reyes. Tr. 106. Specifically, Dr. Shinnar disagreed with Dr. Castro-Reyes' diagnosis of epilepsy on February 24, 2014, based on R.G.'s clinical course and his initial EEG done January 29, 2014. Id.; see Pet. Ex. 5 at 416-19.

A treating physician's opinions are considered "quite probative," and are entitled to some weight. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1326 (Fed. Cir. 2009); Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence since they are created contemporaneously with the treatment of the vaccinee. Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993).

The undersigned defers to the diagnosis of R.G.'s treating physician, Dr. Castro-Reyes, and finds that Dr. Castro-Reyes' diagnosis of epilepsy was appropriate and correct at the time that she made the diagnosis on February 24, 2014.

D. Causation Analysis

The petitioners assert that the vaccinations R.G. received on November 15, 2013, caused a febrile seizure which triggered the process by which he developed epilepsy. Both Dr. Huq and Dr. Shinnar agree that the vaccinations R.G. received on November 15, 2013, likely caused his initial seizure. Tr. 85, 120. They disagree, however, as to whether that initial seizure caused or contributed to the development of his epilepsy. Dr. Shinnar testified that whether a febrile seizure is the "starting point" of epilepsy is a much debated issue. Tr. 114. However, he does agree that in rare cases, patients with febrile seizures can develop epilepsy. Tr. 115.

1. Althen Prong One

Under Althen Prong One, petitioners must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioners' theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; Boatmon, 941 F.3d at 1359; see also Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d at 1347 ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

From a chapter authored by Dr. Shinnar, he quotes data showing that in "children with febrile seizures[,] . . . epilepsy subsequently develops in 2-10 percent." Resp. Ex. E at 6. There is a "slightly but statistically significant increased risk of subsequent epilepsy" after febrile seizures. Id. at 7. This risk is increased to 5-10% where the febrile seizure is a complex or focal seizure. Tr. 123.

Dr. Huq explained the mechanism by which epilepsy is thought to occur following an initial vaccine-induced febrile seizure. See Pet. Ex. 13 at 5-9. Pro-inflammatory cytokines are produced in response to vaccinations. Id. at 5. These cytokines lead to an inflammatory state in the brain, which causes enhanced neuronal excitability and contributes to a disruption of the blood brain barrier. Id. Some of the pro-inflammatory cytokines are involved in the "precipitation of seizures," while others are implicated in the process by which the brain becomes predisposed to recurrent seizures. Id. at 2. While the exact cause of epilepsy is not

clear, genetic factors are also thought to be at play. Pet. Ex. 15 at 1. "A genetic predisposition to develop sustained inflammatory reactions" has been suggested in children with febrile seizures. Id. at 2. It is thought that genetic factors play a role in decreasing the seizure threshold by either activating excitatory pathways or by disturbing inhibitory systems. See Resp. Ex. J at 2.[11] "[B]rain inflammation is associated with the breakdown in the [blood brain barrier], and [blood brain barrier] leakages ha[ve] been implicated both in the induction of seizures and in the progression to epilepsy." Pet. Ex. 13 at 6. A seizure can cause blood brain barrier ("BBB") leakage. See Tr. 52-53, 75-77.

Dr. Shinnar explained the mechanism of the development of epilepsy in a manner similar to Dr. Huq. Dr. Shinnar agreed that pro-inflammatory cytokines are produced in response to vaccination and that the cytokine profile IL-beta affects neuronal excitability. Tr. 108. He also agreed that brain inflammatory processes contribute to a decrease in the seizure threshold. Tr. 109.

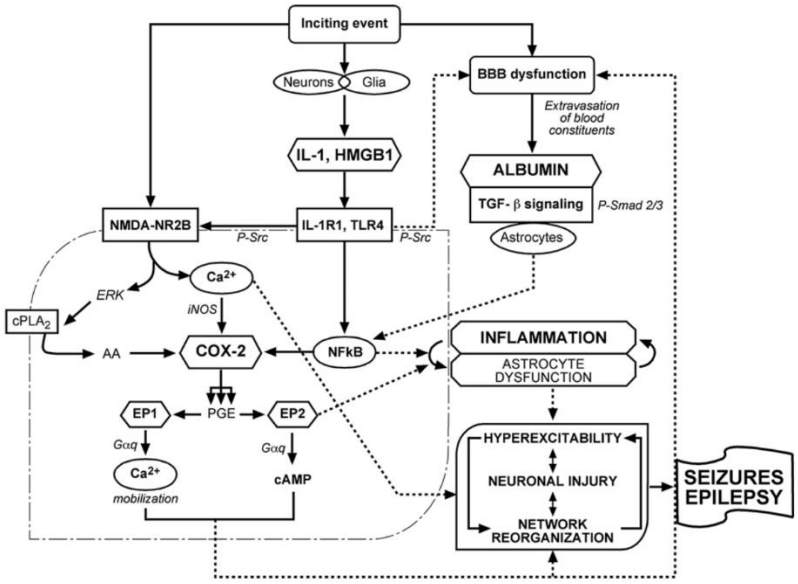
The central question for Dr. Shinnar is whether febrile seizures cause or contribute to the development of epilepsy or whether they are simply markers for epilepsy. Tr. 111-12. According to Dr. Shinnar, only prolonged seizures can initiate or contribute to the development of epilepsy. Tr. 110-11. The undersigned finds that based on the opinions of Dr. Huq, along with the medical literature filed by both parties, in rare cases, a brief febrile seizure triggered by vaccinations can be the starting point for the development of epilepsy.

For example, in the Doose article, the authors state that, in rare cases, febrile seizures form the starting point of epilepsy by activation of excitatory pathways or disturbance of inhibitory systems. Resp. Ex. J at 7. Other factors, such as genetics, may also play a role. See Tr. 45, 114. In the Pitkanen article, the authors explain that "[i]n animals, it has been shown that even brief induced or spontaneous seizures, in addition to [status epilepticus], can trigger neurogenesis." Pet. Ex. 13, Tab TT at 3. And in the Virta article, the authors opine that "[c]hildren with febrile seizures may therefore have an increased pro-inflammatory reaction during fever," which "may predispose some children to the development of epilepsy." Pet. Ex. 13, Tab LLL at 1.[12]

[11] H. Doose et al., EEG Longitudinal Studies in Febrile Convulsions, 14 Neuropediatrics 81 (1982).

[12] Miia Virtua et al., Increased Frequency of Interleukin-1Beta (-511) Allele 2 in Febrile Seizures, 26 Pediatric Neurology 192 (2002).

The mechanism is illustrated below:



Pet. Ex. 13, Tab JJJ at 2 fig.1.[13] In the schematic illustration above, Vezzani and her co-authors defined the phrase "inciting event" as an event with "epileptogenic properties." Id. Examples of inciting events were listed and specifically included "febrile seizures." Id.

During the hearing there was discussion about whether a brief febrile seizure could disrupt the BBB and contribute to the development of epilepsy. Van Vliet et al. describe that in an animal model, "it has been shown that a single bicuculline-induced[14] seizure is sufficient to compromise the BBB." Pet. Ex. 13, Tab FFF at 6.[15] In another article by Van Vliet et al., the authors opine that there is "ample evidence from experimental animal studies that BBB dysfunction can be caused by seizure activity . . . [and] that BBB disruption can also lead to epilepsy." Pet. Ex. 13, Tab GGG at 1.[16] They were able to show that a "long lasting increase in BBB permeability [occurred] after a single seizure." Id. at 2. Further, they state that although BBB leakage gradually decreases, it can persist even weeks or months after the initial insult. Id. at 4.

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[13] Annamaria Vezzani et al., The Role of Inflammation in Epileptogenesis, 69 Neuropharmacology 16 (2013).

[14] Bicuculline is a neurotoxin that is a convulsant. Bicuculline, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=6028&searchterm=bicuculline (last visited Mar. 15, 2021).

[15] E.A. Van Vliet et al., Role of Blood-Brain Barrier in Temporal Lobe Epilepsy and Pharmacoresistance, 277 Neuroscience 455 (2014).

[16] E.A. Van Vliet et al., Blood-Brain Barrier Dysfunction, Seizures and Epilepsy, 38 Seminars Cell & Developmental Biology 26 (2015).

These articles support Dr. Huq's theory of why and how a febrile seizure caused by vaccinations can cause changes in the brain that contribute to the development of epilepsy. Accordingly, the undersigned finds that petitioners have set forth a sound and reliable medical theory, satisfying Althen Prong One.

2. Althen Prong Two

Under Althen Prong Two, petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

The petitioners need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Here, both experts agree that the vaccinations likely caused R.G.'s initial seizure. The undersigned has found that petitioners presented a sound and reliable theory as to how, in rare cases, a febrile seizure can trigger changes in the brain that can lead to epilepsy. Here, the undersigned extends that finding to R.G., and holds that R.G.'s vaccinations caused his initial febrile seizure which caused or contributed to changes in the brain that caused his epilepsy.

R.G. had his first seizure on November 15, 2013, within 24 hours of his vaccinations. Pro-inflammatory cytokines were released after these vaccinations, causing fever, and the initial seizure. Of note, R.G. received the flu vaccine in addition to the nine childhood vaccines he was scheduled to receive. R.G. had his next seizure nine weeks later. After the second seizure, his EEG was abnormal and consistent with epilepsy. R.G. was diagnosed with epilepsy and put on anticonvulsants. This chronology suggests that R.G. had changes in the brain after his initial seizure, which caused or contributed to his second seizure, as well as the abnormalities seen on his initial EEG. Specifically, the EEG showed a focal epileptogenic process in the "right parieto posterior temporal occipital and left occipital regions." Pet. Ex. 5 at 389-90. As described by Dr. Huq, the time frame from seizure onset to the diagnosis of epilepsy was just over two months. This clinical course is consistent with the effect of the pro-inflammatory cytokines released after vaccination, affecting neuronal excitability, and creating changes in the brain that caused epilepsy. The fact that R.G. received the flu vaccine along with the other vaccines increased the risk of his initial febrile seizure. Tr. 30-32.

Dr. Shinnar agreed that R.G.'s initial seizure "may well have been related" to the vaccines administered to him on November 15, 2013. Tr. 84. However, Dr. Shinnar characterized it as a "benign febrile seizure." Tr. 85. While the literature states that most febrile seizures are benign, it is also clear that not all febrile seizures are harmless.

Dr. Shinnar agreed that fever after vaccination is caused by cytokines. In particular, Il-1beta is responsible for producing fever. It is also known to be a pro-convulsive that lowers seizure threshold. Tr. 88-89. The cytokine profile is what leads to a seizure. With fever, the profile is primarily IL-1beta cytokine. Tr. 90-91. Cytokines stay in the system after seizure. Dr. Shinnar explained that after prolonged febrile seizures, a sequence of events involving cytokines, which cause chronic inflammation, can contribute to the development of epilepsy.[17] Tr. 91-92. Dr. Shinnar does not believe these changes can occur after a brief febrile seizure. Instead, he argued that they only occur after prolonged seizures or status epilepticus. However, as briefly discussed above, relative to Althen Prong One, medical literature specifically identifies febrile seizures as potential triggers for epilepsy. These articles support Dr. Huq's position that in rare cases, a febrile seizure can lead to changes in the brain, as happened here.

The second reason for the undersigned's finding as to Prong Two, is that R.G.'s initial seizure had characteristics of a complex seizure, which increased his risk of developing epilepsy. Dr. Huq explained that the "initial seizure was characterized by unusual vocalization, stiffening of the trunk and extremities, slow breathing, cyanosis, and unresponsiveness." Pet. Ex. 15 at 1; see also Tr. 13. Dr. Huq testified that based on the fact that R.G.'s subsequent seizure was similar in character to the initial one, and the fact that his EEG showed focal abnormalities, it is more likely than not that R.G.'s initial vaccine related seizure was also a focal (complex) seizure. Tr. 73. This increased the risk that R.G. would develop epilepsy. Tr. 74.

Dr. Shinnar testified that there was no way to know whether R.G.'s initial seizure was focal, and thus, complex. Tr. 129. Even if R.G.'s first seizure was focal, that did not change Dr. Shinnar's opinion as to causation. Tr. 133. However, Dr. Shinnar agreed with Dr. Huq that a focal seizure increases the risk of epilepsy. Id. Thus, there is evidence that R.G.'s initial vaccine related seizure was focal and thus complex, and as such, his risk of epilepsy was higher.

The third reason for the undersigned's finding as to Prong Two, is that there was no alternative cause identified for R.G.'s epilepsy. As explained by Dr. Huq:

> The pregnancy and delivery were uncomplicated. [R.G.] did not have any trauma or any genetic syndromes or past medical problems that would predispose him to develop epilepsy. Family history was negative on both paternal and maternal sides with regards to epilepsy or any neurodevelopmental disorders. His brain MRI did not show any developmental anomaly, cortical dysplasia or brain malformation. Sodium channel mutation (SCN1A gene mutations) have been identified in some individuals as a cause of epilepsy after vaccination. The treating physicians of [R.G.] did not think SCN1A gene mutation as a likely cause of [R.G.'s] epilepsy and chose not to perform the genetic testing for SCN1A. Seizures associated with SCN1A mutations are aggravated by sodium channel blockers like Trileptal (Wirrell, 2016). However, [R.G.'s] seizures were

[17] Dr. Shinnar further opined, however, that the cytokines present at the time of a febrile seizure would not be present nine weeks later. Tr. 91. He further stated that the cytokine IL-1beta was not involved in chronic inflammation. Tr. 92.

controlled with Trileptal which makes it unlikely that he has a SCN1A gene mutation.

Pet. Ex. 13 at 9.

R.G. had had two MRI studies. The first one was done March 10, 2014. Pet. Ex. 5 at 348. The report mentioned a possible T2 flare change that could represent an artifact, however Dr. Huq testified that he would have considered the study normal. Tr. 49. Dr. Shinnar testified that it was possible that the MRI was abnormal, but his opinion did not rise to the level of more likely than not. Tr. 95.

The second MRI was performed on May 28, 2019, and it was also interpreted as normal. Tr. 49. Dr. Huq testified that it did not show cortical dysplasia, stroke, mass lesion, or vascular lesions. He testified that these two normal MRIs ruled out a host of causes of epilepsy. Id. Dr. Shinnar testified that if R.G.'s second MRI was normal, the cause of R.G.'s epilepsy was unknown, which he opined was true for the majority of cases of epilepsy. Tr. 102. Therefore, the diagnostic work-up and MRIs did not provide any evidence of an alternative cause.

The last reason for the undersigned's finding is based on the appropriate temporal association between R.G.'s vaccinations and his initial seizure, as well as the time frame from his initial seizure to his diagnosis of epilepsy, discussed below.

For these reasons, the undersigned finds that petitioners, by preponderant evidence, have shown that the vaccinations were the cause for R.G.'s initial seizure and epilepsy. Accordingly, petitioners have satisfied Althen Prong Two.

3. Althen Prong Three

Althen Prong Three requires petitioners to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been equated to mean a "medically acceptable temporal relationship." Id. The petitioners must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disease's etiology, it is medically acceptable to infer causation-in-fact." De Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 542 (2011), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013).

Dr. Huq opined that for the DTaP and flu vaccinations, the onset of R.G.'s initial seizure was appropriate. Tr. 50-51. Dr. Shinnar agreed that a seizure occurring within 24 hours of vaccinations was a medical appropriate time frame to infer a causal relationship. Tr. 120. Thus, there is expert agreement that there was a proximately temporal relationship between R.G.'s vaccinations and his initial seizure.

The next question is whether the time frame between R.G.'s initial seizure and the development of his epilepsy was appropriate. Dr. Huq opined that R.G.'s initial seizure began the process of epileptogenesis—the process by which R.G. developed epilepsy. Tr. 18. When R.G. was seen by Dr. Castro-Reyes after his first EEG, she diagnosed him with epilepsy based on his clinical course and abnormal EEG. Tr. 20. Dr. Huq testified that this time frame of nine weeks was appropriate in terms of epileptogenesis. Tr. 51.

Dr. Huq cited the 2015 Van Vliet article to support his opinion. In that article, the authors concluded that BBB leakage may continue for weeks to months after an initial insult such as a seizure. Pet. Ex. 13, Tab GGG at 1. This sustained dysfunction of the BBB leads to an altered micro-environment of neurons with increased excitability and lowered firing threshold that contribute to the emergence of seizures. Tr. 52-53 (citing Pet. Ex. 13, Tab GGG at 1.)

Further, the undersigned notes that R.G.'s treating neurologist routinely documented that the onset of his seizure disorder was the date of his vaccinations and initial seizure, November 15, 2013. See Tr. 118.

For the above reasons, the undersigned finds that petitioners have provided preponderant evidence of a proximate temporal relationship between R.G.'s November 15, 2013 vaccinations and his initial seizure, as well as his epilepsy.

E. Alternative Causation

Because the undersigned concludes that petitioners have established a prima facie case, petitioners are entitled to compensation unless respondent can put forth preponderant evidence "that [R.G.'s] injury was in fact caused by factors unrelated to the vaccine[s]." Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). As discussed above, respondent did not prove by a preponderance of evidence that R.G.'s injury was "due to factors unrelated to the administration of the vaccine[s]." § 13(a)(1)(B).

IV. CONCLUSION

For the reasons discussed above, the undersigned finds that petitioners have established by preponderant evidence that they are entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master