In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. [redacted] V
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To be Published

JOHN DOE 79, and JANE DOE 79, as parents and natural guardians of CHILD DOE 79,	*	
Petitioners,	*	
v.	*	Entitlement; DTaP; neuroblastoma; opsoclonus-myoclonus syndrome
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Anne C. Toale, Sarasota, FL, for petitioners.
Voris E. Johnson, Jr., Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioners filed a petition on June 2, 2008 under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10 et seq., alleging that their daughter CHILD DOE 79 (hereinafter,

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would constitute a clearly unwarranted invasion of privacy. When such a decision is filed, petitioners have 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.

"CHILD DOE 79") received DTaP[2] on May 17, 2005 when she was 19 months old, which significantly aggravated her abdominal neuroblastoma,[3] resulting on June 9, 2005 in opsoclononus myoclonus syndrome (OMS),[4] also known as Kinsbourne's syndrome.[5] They allege that each factor, the vaccination and the neuroblastoma, was significant in causing CHILD DOE 79's OMS. In the alternative, petitioners allege that DTaP caused CHILD DOE 79's OMS.

The leading doctor involved with treatment of and research in OMS, Dr. Michael R. Pranzatelli, whom CHILD DOE 79 saw on July 14, 2005, wrote a letter to CHILD DOE 79's pediatric neurologist, Dr. Yasmin Khakoo on July 15, 2005, stating that CHILD DOE 79 had no antecedent illness before her OMS and her most recent immunization had been one month previous to her manifestation of OMS. Med. recs. at Ex. 5, p. 3. CHILD DOE 79's neuroblastoma was surgically removed, although CHILD DOE 79 retained significant problems, including rage attacks, inability to sit or walk, tremulousness, shaking spells, lack of speech, and low muscle tone. Id. at 3-4. Dr. Pranzatelli's opinion was that CHILD DOE 79 had severe OMS

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[2] DTaP is "a combination of diphtheria toxoid, tetanus toxoid, and [acellular] pertussis vaccine...." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1998.

[3] A neuroblastoma is a "sarcoma consisting of malignant neuroblasts, usually arising in the autonomic nervous system ... or in the adrenal medulla...." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1253. A neuroblast is "any embryonic cell that develops into a nerve cell or neuron." Id.

[4] OMS is "a syndrome of movements of the eyes (opsoclonus) and trunk (myoclonus), occurring in conjunction with a number of conditions...." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1827.

[5] Kinsbourne's syndrome is "myoclonic encephalopathy of childhood...; characterized by myoclonus of trunk and limbs and by opsoclonus, with ataxia of gait and intention tremor; some cases have been associated with occult neuroblastoma." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 611, 1822.

as a result of her neuroblastoma. Id. at 5. He recommended ACTH[6] to eliminate cerebrospinal fluid B cells as they had the clearest role in the pathophysiology of OMS. He also recommended that CHILD DOE 79 not receive any immunizations for a minimum of two years after completion of all immunotherapy. He wrote in the letter that he told CHILD DOE 79's parents that CHILD DOE 79 should never receive any live virus injections or grouped immunizations.[7] He also told the parents that they and CHILD DOE 79's normal sibling should receive flu vaccine each year, but that CHILD DOE 79 should not. Id.

A hearing was held on September 3, 2009. Testifying for petitioners was Dr. Marcel Kinsbourne. His opinion is that the vaccine and the neuroblastoma were co-stimulants of CHILD DOE 79's OMS. Testifying for respondent was Dr. Michael E. Cohen. His opinion is that the neuroblastoma alone caused CHILD DOE 79's OMS.

TESTIMONY

Dr. Marcel Kinsbourne, a pediatric neurologist, testified for petitioners. Tr. at 5. He defined OMS as arising in infancy typically between nine months of age and two years. It is neurological, characterized by sharp myoclonic muscle jerks that are irregular and unpredictable. Tr. at 6. The muscle jerks affect not only the body, but also the direction of the child's gaze. The child's eyes point irregularly in a variety of directions. Because the eyes move in tandem, we know the impulses are coming from the brainstem. OMS is a disorder of muscle control.

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[6] ACTH is "adrenocorticotropic hormone." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 22.

[7] Dr. Pranzatelli defined "grouped immunizations" as, e.g., DPT. Med. recs. at Ex. 5, p. 2. Once CHILD DOE 79 had completed immunotherapy for no less than two years, she could have grouped immunizations spread out at six-month intervals. Id.

Not only does this result in jerking but also in ataxia, meaning the child has great difficulty controlling his or her movements. He or she really cannot walk. Tr. at 7.

Dr. Kinsbourne published the first description of this condition in an article in 1962 entitled "Myoclonic Encephalopathy of Infants." Tr. at 8. This was filed as Exhibit 26 in the case. Id. The condition has been named Kinsbourne's syndrome. Id. In many of the cases, there is an associated neuroblastoma. Tr. at 9. A neuroblastoma is a solid tumor composed of nerve cells and is the most common tumor in infants. It is a tumor of the sympathetic nervous system, which is one wing of the autonomic nervous system. Id.

A specific society in England, called the Dancing Eyes Society, has been formed and Dr. Kinsbourne has given keynote addresses to it. A similar society is being formed in the United States and he will be the keynote speaker there. Tr. at 10. Even though 50 percent of OMS patients have a neuroblastoma, only one to three percent of children with neuroblastomas also have OMS. Tr. at 11. Dr. Kinsbourne's explanation is that there must be something precipitating the tumor to cause OMS. Id. Neuroblastoma is common while OMS is rare. Tr. at 12.

In most if not all cases of neuroblastoma, the individual's immune system mounts an attack on the tumor which may cause the tumor to regress and disappear. Id.

The usual point of view with which Dr. Kinsbourne agrees is that OMS, like most immune disorders, can be triggered by more than one type of antigen and reaction. Tr. at 14. A reaction against a neuroblastoma may generalize to the cerebellum of the brain. There is little doubt that reactions to quite mundane infections or immunizations can also do that in susceptible individuals. Id. OMS is a consequence of an immune-mediated attack on the cerebellum. Id.

Dr. Kinsbourne's opinion is that CHILD DOE 79's DTaP caused her OMS. Tr. at 16. Her neuroblastoma developed before she showed her first OMS symptoms. CHILD DOE 79's immune system mounted a subclinical immune attack against the neuroblastoma. The DTaP up-regulated the immune attack to a point where it spread so as to involve not only the tumor cells, but also the cerebellum, destroying nervous tissue there and causing the onset of OMS. The best way Dr. Kinsbourne thinks about it is that two interacting causes, a double hit, conspired to set up CHILD DOE 79's condition. Id.

By "up-regulated," Dr. Kinsbourne means causing the activation of a larger population of T-cells which then spread to attack not only the initial target antigen, but also other antigens in the cerebellum. Tr. at 17. Both the neuroblastoma and the DTaP were substantial factors in causing CHILD DOE 79's OMS. Id. If CHILD DOE 79 had not received DTaP, she would not have had the OMS attack she had. Whether she would have had OMS at some other time, he has no way to know. Id. She was almost outside the age range when OMS usually happens because she was nearly two years old. Tr. at 17-18.

Dr. Kinsbourne stated that Dr. Pranzatelli is very knowledgeable about OMS and has spent much of his professional career working with children who have OMS. Dr. Pranzatelli wrote important articles on OMS, including a case study in which Dr. Kinsbourne was a co-author. Tr. at 19. Dr. Pranzatelli warns parents not to permit their children who have OMS to receive DTaP. Tr. at 20. Dr. Kinsbourne stated:

> Now, the reason that he warns parents not to have that vaccination is the very same reason as that which I believe caused the OMS in the first place, an up-regulating of the immune system. So what he's saying is these children's immune systems have been already up-regulated causing the disease, and the last thing we want is to up-regulate them any more.

Id.

Dr. Kinsbourne agrees with Dr. Pranzatelli's warning about a child with OMS not receiving DTaP. Id. OMS is a condition that is quite apt to relapse when a further immune challenge is imposed on the child with a viral or bacterial infection. Tr. at 20-21. If the child's immune system had been normal, it would have properly reacted to the neuroblastoma when it first began to develop. Tr. at 21. The problem is not only in the neoplasm (the tumor itself), but also somewhere else in the body. Tr. at 22. Paraneoplastic neurological disorders are quite common in adults, but this is the only type of paraneoplastic disorder documented in young children. Id.

People with deficient immune systems are more apt to have autoimmune disorders than people with healthy immune systems. Tr. at 24. In the two-hit process, the first hit is by the immune system against the tumor, which is useful, and the second hit is against the child's brain, which is harmful. Tr. at 25. When CHILD DOE 79 received DTaP, the presenting antigen was already there because the neuroblastoma was already there, and the vaccine up-regulated the existing reaction. Tr. at 26. Since only one to three percent of children with neuroblastoma develop OMS, there has to be some exposure to a subsequent antigen from an infection or vaccination which promotes an overdrive in the immune system to cause the OMS. Tr. at 29. Once the process is unleashed, it takes on a life of its own. Tr. at 30. Even though the neuroblastoma is surgically removed, as it was in CHILD DOE 79's case, the surgery does not stop the OMS. Id.

Dr. Pranzatelli wrote that immunizations designed to boost the immune system against specific antigens which are given repetitively and overlap with the mean age of onset of OMS

initially activate T-cells (generalized activation), a process which may last several weeks. Tr. at 31. The young immune system is more easily primed. Id.

Dr. Kinsbourne thinks that one month between vaccination and onset of OMS is an appropriate interval to show causation. Tr. at 33. Dr. Pranzatelli wrote that immunizations are a reasonable mechanism for co-stimulation. Tr. at 34. Dr. Kinsbourne has treated 15 or 20 cases of OMS in his career and consulted on many more. Tr. at 38.

Dr. Kinsbourne believes it is the tetanus element in the DTaP which is co-stimulating the OMS. Tr. at 51. Pertussis tends to be neurotoxic and fairly immediate, its effects occurring in the first 72 hours. Tr. at 52. Tetanus' immune-mediated effects tend to be between five and 42 days, often in the second or third week after vaccination. Id. The diphtheria element appears harmless. Id.

Dr. Kinsbourne stated his opinion relies on the mechanisms that Dr. Pranzatelli described in his articles. Tr. at 54. OMS is a neuromediator. Tr. at 62. Immune-mediated neurological disorders are triggered by intercurrent infections. Id. What vaccines and infections have in common is that both provoke immune responses because they have antigens to which the human immune system reacts. Id. There is good reason to believe that infections up-regulate the immune system as Dr. Pranzatelli described, and Dr. Kinsbourne applies that reasoning equally to vaccinations as a mechanism of injury. Id.

When Dr. Pranzatelli advised CHILD DOE 79's parents in this case not to allow her to receive grouped immunizations, he meant immunizations like DPT which have three vaccines in one. Tr. at 83. Dr. Kinsbourne stated that Dr. Pranzatelli has a unique amount of experience treating OMS children. Tr. at 89. Dr. Kinsbourne did not think that when Dr. Pranzatelli wrote

in his record for CHILD DOE 79 that the cause of her OMS was neuroblastoma, Dr. Pranzatelli was excluding her DTaP vaccination as a cause. Tr. at 90. All Dr. Pranzatelli's note means to Dr. Kinsbourne is that Dr. Pranzatelli was distinguishing between OMS with a neuroblastoma and OMS without a neuroblastoma. Id. Doctors do not necessarily put into their diagnosis antecedents which quite likely precipitated the illness. Id. Here, the diagnosis was neuroblastoma-type OMS. Id. CHILD DOE 79's other treating physicians did not identify her DTaP as the cause of her OMS, attributing it to her neuroblastoma, but that does not mean the OMS did not have the vaccine as a trigger. Tr. at 92.

Dr. Kinsbourne agrees that neuroblastoma can result in OMS without a vaccination, but he thinks there would be other triggering factors. Tr. at 94, 95. The timing between CHILD DOE 79's DTaP and the onset of her OMS was one factor in Dr. Kinsbourne's opinion. Tr. at 97. Had the interval been three or four months instead of 23 days, he would not have come to the same conclusion. Id. His understanding of OMS is that it takes two hits or causal factors to cause it. Tr. at 100. He does not believe that a neuroblastoma by itself is sufficient to cause OMS. Id. OMS is one of many types of immune-mediated disorders that is set off by challenges to the immune system. Tr. at 101. Neuroblastoma itself triggers a response by the immune system. Id. Dr. Pranzatelli wrote that the main co-stimuli that empower an immune response are virus, tumor, and vaccine. Tr. at 103. He also wrote that an antigen may not stimulate an immune response unless co-stimulation has occurred. Id.

Dr. Michael E. Cohen, a pediatric neurologist, testified for respondent. Tr. at 106. His opinion is that the most likely cause of CHILD DOE 79's OMS is her neuroblastoma. Tr. at 109. OMS is the only paraneoplastic syndrome well-recognized in childhood. Id. He congratulated

Dr. Kinsbourne for his insightful descriptions of OMS in 1962, making the medical profession aware of the problem, and 47 years later, Dr. Kinsbourne's name is still attached to the illness, but the knowledge of OMS has not progressed much further in that time. Tr. at 111.

In 50 percent or more of patients with OMS, there is an associated neuroblastoma. Tr. at 112. That alone suggests a cause and effect relationship. Id. The theory underlying the connection is that the neuroblastoma produces an autoimmune process in which the body turns against itself in parts of the brainstem and cerebellum. Id. Dr. Cohen does not think there is strong evidence that someone needs an antecedent or subsequent cause to produce OMS when someone has a neuroblastoma. Tr. at 113. Dr. Kinsbourne's second-hit theory is not generally accepted in the pediatric neurology community. Id. Dr. Cohen finds Dr. Kinsbourne's view of vaccines as causal of OMS when neuroblastoma is present highly speculative. Id. He queries why Dr. Kinsbourne and Dr. Pranzatelli are the only ones in the world of immunology, child neurology, and allergy focused on this approach. Id. Dr. Cohen finds the co-stimulation mechanism speculative. Tr. at 114.

He agreed that the Stefanowicz article, in case 1, which described a girl having OMS two days after measles vaccination might suggest causation from the vaccine. Tr. at 117, 118. But a neuroblastoma was not discovered until six years later. Therefore, this article would not affirm co-stimulation. Tr. at 118, 119. There are only 650 cases of neuroblastoma in the US each year. Tr. at 119-20. If vaccinations were co-stimulants with neuroblastoma, then since all children are vaccinated, there should be a much higher percentage of children with neuroblastoma who develop OMS than the small percentage of children with neuroblastoma who develop OMS now.

Tr. at 120. CHILD DOE 79's OMS is sufficiently explained by her neuroblastoma alone. Tr. at 122.

Dr. Cohen has treated from five to seven OMS patients. Tr. at 125. He treated them with ACTH, steroids, and IVIG. Id. He administered these treatments on the assumption that OMS is autoimmune. Id. However, that does not mean it is proven that OMS is autoimmune. Tr. at 125-26. People assume there is an OMS antigen because of the assumption that OMS is an autoimmune phenomenon. Tr. at 129. The theory is that OMS antigen provokes the formation of an antibody that is directed against parts of the brainstem, but Dr. Cohen stated it has not been proven. Tr. at 130.

Dr. Cohen accepts that Dr. Pranzatelli has spent a great deal of his career in OMS and knows a great deal about it, but many people disagree with his interpretation of OMS. Tr. at 139. Dr. Cohen agrees that OMS is generally accepted as an autoimmune disease, but he does not think it is scientifically proven to be an autoimmune disease. Tr. at 140.

Other Submitted Material

Petitioners filed 34 articles into the record. Among them is Exhibit 26, the seminal article that linked Dr. Kinsbourne's name to OMS: "Myoclonic encephalopathy of infants" by M. Kinsbourne, 25 J Neurol Neurosurg Psychiat 271-76 (1962). (Petitioners also filed this article as Exhibit 37.) Of the six case children Dr. Kinsbourne discusses, the first case child had an upper respiratory tract infection two months before onset of OMS; the third case child had nasal catarrh, a mild cough, and a triple vaccination one month before onset of OMS; the fourth case child had onset of OMS during a mild illness with vomiting and diarrhea; and the fifth case child had onset of OMS during a mild illness with fever and rash and, one week after receiving

polio vaccine, her OMS was exacerbated. The second and sixth case children had no known antecedent infections or vaccinations. Id. at 271-74. Dr. Kinsbourne posits that myoclonic encephalopathy is an allergic manifestation and that viral infections and immunizations "set up a self-perpetuating auto-immune process lasting for years." Id. at 276.

Petitioners filed as Exhibit 27 an article entitled "Long-term outcome in children with opsoclonus-myoclonus and ataxia and coincident neuroblastoma" by P.S. Koh, et al., 125 J Pediatr 712-16 (1994). The authors state that two percent of children with neuroblastoma are seen because of OMS. Id. at 712.

Petitioners filed as Exhibit 29 an article entitled "Neurological sequelae of the dancing eye syndrome" by K.R.E. Pohl, et al., 155 Eur J Pediatr 237-44 (1996). The authors studied 54 patients with dancing eye syndrome (another name for OMS). Five of the children had been immunized within four weeks of onset: four with measles vaccine and one with DPT vaccine. Id. at 238. Fifty percent of the 54 children had an associated intercurrent infection at the outset, over half of which were of the upper respiratory tract. Id. at 242. Four of the 54 children had malignant disease. Id. at 238. Three of those four children had a neuroblastoma. Id. at 239. Only two to three percent of children with neuroblastoma also have OMS. Id. at 241.

Petitioners filed as Exhibit 31 an article entitled "Long-Term Neurologic Outcome in Children With Opsoclonus-Myoclonus Associated with Neuroblastoma: A Report from the Pediatric Oncology Group" by C. Russo, et al., 29 Med & Ped Oncology 284-88 (1997). The authors state that three percent of children with neuroblastoma have OMS. Id. at 284. They also state that there is evidence that the pathophysiology of OMS is immune-mediated. Id. at 288.

Petitioner filed as Exhibit 41 an article entitled "Forty-One-Year Follow-Up of Childhood-Onset Opsoclonus-Myoclonus-Ataxia: Cerebellar Atrophy, Multiphasic Relapses, and Response to IVIG" by M.R. Pranzatelli, et al. (Dr. Kinsbourne is a co-author), 17 Movement Disorders 6:1387-90 (2002). The article discusses one of the six children (the third case child) in Dr. Kinsbourne's 1962 seminal article on myoclonic encephalopathy in children, the article which resulted in OMS becoming known as Kinsbourne's syndrome. The case child was 42 years old at the time this follow-up was written. At 11 months of age, he was diagnosed with OMS one week after he received DPT vaccine and had an apparent viral illness. Id. at 1387. After treatment with ACTH for 11 years, he was in remission for 10 years. At the age of 22, he had a relapse after a flu-like illness. Id. at 1388. It was unclear if the case individual had neuroblastoma. Id. at 1390. He did not have three of the autoantibodies found in a minority of patients with a paraneoplastic syndrome. Id.

Petitioners filed as Exhibit 43 excerpts from the National Pediatric Myoclonus Center website. The immunization facts on page 2 state: "Although pertussis immunization is now available in an acellular form (DTaP), which causes less cross-reactivity, we don't recommend giving children with OMS any pertussis-containing preparation." It also states "Immunization can make OMS worse." Further, the immunization fact page states: "Immunizations tend to stimulate the immune system. In OMS, the immune system is already overactive and needs to be suppressed, not further stretched." Id.

Petitioners filed as Exhibit 46 an article entitled "Review. The Neurobiology of the Opsoclonus-Myoclonus Syndrome" By M.R. Pranzatelli, 15 Clin Neuropharmacology 3:186-228 (1992). Dr. Pranzatelli states: "Opsoclonus-myoclonus is a syndrome, not a single disease,

which also may be induced by drugs and toxins, metabolic disorders, congenital and degenerative disorders, and infections." Id. at 211.

Petitioners filed as Exhibit 47 excerpts from Dr. Pranzatelli's OMS website explaining what goes wrong in autoimmune diseases. Dr. Pranzatelli states: "An antigen may not stimulate an immune response unless *co-stimulation* has occurred. The main co-stimuli that empower an immune response are: virus, tumor, vaccine [emphasis in original]." Id. at 4.

Respondent filed as Exhibit C an article entitled "Neuroblastoma and opsoclonus-myoclonus-ataxia syndrome - clinical and pathological characteristics" by J. Stefanowicz, et al., 46 Folio Neuropathologica 3:176-85 (2008). The authors state:

> Paraneoplastic neurological syndromes are immunologically driven processes. ... Opsoclonus-myoclonus-ataxia (OMA) syndrome is the most common paraneoplastic neurological syndrome of childhood. ... OMA is a rare neurobehavioral paraneoplastic disorder found in less than 4% of patients with neuroblastoma (NB). ... The pathogenesis of OMA is still unclear, although the presence of anti-neuronal antibodies against unknown membrane antigens of neuroblastoma cells and cerebellar neurons suggests that the disorder is immunologically mediated. ... [T]he pathogenesis of OMA might be an autoimmune phenomenon mediated by antibodies cross-reacting with antigens on neuroblasts and on neuronal cells in the cerebellum and the brain stem.

Id. at 176, 177.

The authors studied four children diagnosed with peripheral neuroblastic tumors, all of whom underwent surgery to remove their tumors. Id. at 177. The first patient was a 15-month-old girl who received a measles vaccination and, two months later, had rapidly intensifying generalized myoclonias, ataxia, balance impairments, and nystagmus. Id. She was diagnosed with Kinsbourne's syndrome. The doctors searched for but did not find a neuroblastoma. Six

years after the onset of her OMA, a mature ganglioneuroma was discovered. Id. at 178. Every infection the girl has exacerbates her OMA symptoms. Id. at 179.

The second patient was a 16-month-old girl who received haemophilus B influenza (HiB) vaccine and was hospitalized due to nystagmus and impaired balance. She was diagnosed with allergic neurological reaction caused by HiB vaccine. Id. Two months after the onset of her OMA, a mixed ganglioneuroblastoma/ganglioneuroma was discovered. Id. (There is no onset interval between vaccination and onset of OMA indicated in the description of the second child.)

The third patient was a four-year-old boy who had chickenpox the month before he had balance and gait impairments, changes in temper, and reduced muscle tone. Id. at 180. A neuroblastoma was discovered. After steroid treatment and chemotherapy, the boy's OMA was in remission until a year later, when he had a viral infection of the upper respiratory tract, and the symptoms of OMA recurred. Id.

The fourth patient was a three and one-half-year-old girl who had impaired balance, opsoclonus, fine tremor, irritability, and negativism. A neuroblastoma was discovered. Id. at 181. On page 178 of the article, the authors inserted Table 1 showing clinical characteristics of patients with OMA and peripheral neuroplastic tumors. The categorization of data includes "Related to vaccination or infection." The first two children have their recent vaccinations listed. The third child has his recent chickenpox listed. The fourth child has "no" in that category.

The authors state: "OMA syndrome very rarely can also develop in association with viral infections or vaccination or without any noticeable reason." Id. at 183. In idiopathic cases, the

authors assume that OMA could have developed in the course of a neuroblastoma which spontaneously regressed. Id. The authors state:

> An important observation in our group was the fact that in two of the children the onset of OMA was primarily connected with a vaccination, while in one of the patients it was associated with a recent history of chickenpox. This is yet further proof of the immunological pathogenesis of OMA.

Id. at 184. They continue:

> During the rapid onset of the syndrome, activated T-cells are capable of crossing the blood-brain barrier, whence they enter the brain and attack neurons. Pranzatelli found that in the acute phase of OMA a cell-mediated immunological response dominated. ... Based on the analysis of our patients we must emphasise [sic] the fact that in some patients the onset of OMA is related to vaccination or infection.

Id. In their 31 references, the authors cite to Dr. Pranzatelli three times when he is primary author, and one time when he is co-author.

On March 19, 2009, respondent filed a motion to take the deposition of Dr. Pranzatelli. On April 6, 2009, petitioners filed a response objecting to respondent's motion, stating that Dr. Pranzatelli had absolutely no desire to be involved in this or any other case in the Vaccine Program. Petitioners also stated that the undersigned should deny respondent's motion because a deposition forced on Dr. Pranzatelli would harm the physician-patient relationship between CHILD DOE 79 and him. Attached as Exhibit A to petitioners' response is a copy of Dr. Pranzatelli's letter to the undersigned with a copy to petitioners' counsel, dated March 16, 2009. Dr. Pranzatelli is Founder and Director of the National Pediatric Myoclonus Center. He states in his letter that it is his sincere wish not to be involved in the case, and continues:

> I don't have much time left to accomplish what it is I have to do, which is to get kids with opsoclonus-myoclonus the best possible

> treatments. ... I am the sole physician for the National Pediatric Myoclonus Center; there is no other physician to cover for me. I have a heavy clinical workload. As most all of our patients come from out-of-town and book their flights months in advance for appointments, my absence causes hardships for them. I have heavy research obligations to institutions that have funded my research. I am responsible for day-to-day supervision of research employees. Unfinished progress reports and manuscripts sit on my desk with approaching deadlines. I also have on-call and inpatient general clinical duties, medical student and resident teaching assignments, and I run our child neurology program. I strongly object to being put in a situation of aiding and abetting parties who seek financial restitution for what are acts of Providence. God, not vaccines, caused this child's disease. The parents should be thankful she has done so very well. I hope you will not force me to participate in this claim.

Exhibit A to petitioners' response to respondent's motion.

During a telephonic status conference held on April 7, 2009, reflected in an Order filed April 8, 2009, the undersigned denied respondent's motion based on Dr. Pranzatelli's letter stating he refused to cooperate in the litigation. Under section 300aa-12(d)(3)(B) of the Vaccine Act, whether the undersigned permits discovery in these proceedings is solely within her discretion. Here, there was a real risk of damaging the doctor-patient relationship if the undersigned permitted the deposition to go forward. Moreover, if Dr. Pranzatelli refused to answer counsel's questions, a deposition would be futile. There was no prejudice to the parties since each party had its own expert.

The undersigned's denial of respondent's motion to depose Dr. Pranzatelli is consistent with the Federal Circuit's discussion of the same subject in Andreu v. Sec'y of HHS, 569 F.3d 1367, 1383 (Fed. Cir. 2009):

> In most instances,... it is both inadvisable and unnecessary to subpoena the testimony of treating physicians. It would not be in the public interest for the specter of a subpoena to provide

> physicians with a disincentive to treat a vaccine-injured patient or to cause them to be less than forthright in creating medical records assessing the relationship between a vaccine and a patient's injury. ... Requiring treating physicians to testify in Vaccine Act cases is likely to serve only to prolong and increase the adversarial nature of proceedings, contrary to Congress' objective to create a federal compensation scheme under which awards are made to "vaccine-injured persons quickly, easily, and with certainty and generosity." H.R. Rep. No 99-908, at 3 (1986), 1986 U.S.C.C.A.N. at 6344....

Respondent filed as Exhibit E an article entitled "Review. The Immunopharmacology of the Opsoclonus-Myoclonus Syndrome" by Dr. Michael R. Pranzatelli, 19 Clinical Neuropharmacology 1:1-47 (1996). (This is also petitioners' Exhibit 30.) Dr. Pranzatelli states that "circumstantial evidence supports an autoimmune basis for OMS." Id. at 2. In a section entitled "Examining the Components of Autoimmunity in OMS," Dr. Pranzatelli states, "Environmental factors are likely to be very important in OMS, including infecting agents such as viruses or bacteria and immunizations or vaccinations." Id. at 18.

In Table 4, entitled "Hypotheses on the immunopathophysiology of OMS," Dr. Pranzatelli states, "In children, immunization may sensitize immune system to next presenting antigen (two-hit corollary)." Id. at 19. He continues:

> Several factors may contribute to the sequence of events leading to immune system dysregulation in OMS. In children, the immune system may become overactive because of the high frequency of viral infections, which average 10 or more yearly during infancy. Immunizations, which precede the onset of OMS in some pediatric cases, may be another predisposing factor. Immunizations, designed to "boost" the immune system against specific antigens, which are given repetitively and overlap with the mean age of onset of OMS ..., initially activate T cells (generalized activation). The stimulation may last several weeks. This is also a time of increased activity and proliferation in the development of the immune system, reticulendothelial system, and thymus gland, and the young immune system is more easily primed.... These factors may be relevant to pediatric but not adult-onset OMS.

Id. at 20.

In concluding, Dr. Pranzatelli states:

> An abnormality of both humoral and cellular immunity (i.e., both B cells and T cells) is the most attractive hypothesis based on current data available in OMS and abundant information on other autoimmune neurologic disorders. A peripheral induction mechanism involving molecular mimicry or one of several other possible mechanisms leads to immune system dysregulation, which transiently allows otherwise forbidden autoaggression against cross-reactive brain antigens. [I]mmunizations are logical candidates for costimulation in peripheral induction in children....

Id. at 36. Dr. Pranzatelli's article was supported by grants from, among others, the Food and Drug Administration. Id. He has 285 references to source materials in the article. Id. at 37-47.

DISCUSSION

To satisfy their burden of proving causation in fact, petitioners must prove by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. 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 . . . ." Such an approach is inconsistent with the use of circumstantial evidence. *Id.* The Federal Circuit stated in Althen, 418 F.3d 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."

Close calls are to be resolved in favor of petitioners. Capizzano, 1440 F.3d at 1327; Althen, 418 F.3d 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, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. Id. at 1148.

Petitioners must show not only that but for DTaP vaccine, CHILD DOE 79 would not have had the OMS, but also that the vaccine was a substantial factor in bringing about her OMS. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999) (a baby developed a high fever after receiving DPT vaccine; he was also harboring E. coli infection which can cause fever; testimony showed that both the vaccine and the infection were substantial factors in causing his high fever that led to his death; petitioners prevailed because the vaccine was a substantial factor).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, 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.

As for epidemiological support for causation, the Federal Circuit in Knudsen, 35 F.3d at 551, ruled for petitioners even when epidemiological evidence directly opposed causation from DPT vaccine. The case concerned the cause of a baby's encephalopathy after a vaccination. Respondent provided evidence that more encephalopathies are caused by viruses than by vaccines, persuading the special master to rule against petitioners. But the Federal Circuit held that the epidemiologic evidence should not bar petitioners from prevailing. Even though epidemiological evidence supported respondent's view that viruses were more likely to cause encephalopathy than vaccinations, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

In the instant action, Dr. Kinsbourne, who has had the honor of having OMS named after him, testified for petitioners that DTaP provided co-stimulation to CHILD DOE 79's neuroblastoma, resulting in OMS. He derived the theory of co-stimulation from Dr. Michael Pranzatelli, founder and director of the National Pediatric Myoclonus Center, and prolific writer about and researcher and treater of OMS in children. Dr. Pranzatelli warns specifically on his website that OMS children should not be immunized and specifically not with grouped vaccines, such as DTaP, or with pertussis vaccine. The reason is that children with OMS have overcharged immune systems and vaccines make the OMS in these children worse. Consistent with the understanding of OMS supporting Dr. Pranzatelli's warning (as well as his medical articles published in peer-reviewed journals), Dr. Kinsbourne testified that DTaP upregulated CHILD DOE 79's immune system, and together with her neuroblastoma, caused her OMS.

Although only one to three percent of individuals with a neuroblastoma have OMS, about 50 percent of children with OMS have a neuroblastoma. It may be that more OMS children have had at one time a neuroblastoma, but the tumor was destroyed due to the immunological attack on it within the child. Dr. Kinsbourne testified that had it not been for the administration of DTaP up-regulating CHILD DOE 79's immune system causing OMS, her neuroblastoma might have been destroyed and she would never have had OMS. She was just reaching the age when children stop manifesting OMS from neuroblastomas when she received DTaP.

Dr. Cohen testified for respondent that there are no animal studies or epidemiologic reports supporting the theory that OMS is an autoimmune disease or that vaccines are a substantial factor in causing OMS. He opined that a neuroblastoma was itself sufficient to cause CHILD DOE 79's OMS and there did not need to be any effect from the vaccination. In

essence, Dr. Cohen seeks the fulfillment of various criteria (animal testing, epidemiologic studies, identification of specific autoantibodies, etc.) in order to prove that OMS is an autoimmune disease and that vaccines can play a role in causing it in a child who, due to a neuroblastoma, is in danger of manifesting OMS. Although this may be the cautious approach of a doctor in the field of medicine, the Federal Circuit has warned special masters not to seek scientific or medical certainty, but only legal probability. Andreu, 569 F.3d at 1380.

The Federal Circuit has also stated that petitioners may prevail without the necessity of providing medical literature, animal studies, and epidemiologic reports. See, e.g., Capizzano. Dr. Cohen's objections are based on the absence of the very materials that the Federal Circuit said petitioners do not need in order to prevail.

Although Dr. Cohen states that Dr. Pranzatelli is not highly regarded in the field of OMS, the undersigned finds his view unpersuasive. The Food and Drug Administration gives Dr. Pranzatelli grants to conduct his research and further his writing on OMS in children. He is a leader in the field and his writing, experience, and research are prolific. He is also a treater for CHILD DOE 79 and it is highly regrettable that respondent sought to depose him because it caused the very tumult that the Federal Circuit warned about in Andreu. The undersigned views Dr. Pranzatelli's distraught statement that the cause of CHILD DOE 79's OMS is God as an indication of how disturbed he was to have litigators pursuing him. Clearly, the doctor wanted nothing to do with litigation. In addition, the fact that in his office records for CHILD DOE 79 he recorded the cause of her OMS as her neuroblastoma does not mean that he thinks DTaP vaccine had nothing to do with it since he was the one who wrote in his website for parents of children with OMS that vaccines may be co-stimulants to induce autoimmune disease, and he

believes OMS is an autoimmune disease. The undersigned does not find persuasive Dr. Cohen's testimony that there is not sufficient proof that OMS is an autoimmune disease in light of repeated medical articles by Dr. Pranzatelli and numerous other authors in peer-reviewed journals stating that OMS is an autoimmune disease, granted we do not have animal studies or know the autoantibodies that affect children with OMS.

Dr. Kinsbourne and Dr. Pranzatelli are far more knowledgeable about OMS than Dr. Cohen. All are pediatric neurologists, but the first (Dr. Kinsbourne) has been the pioneer in the study of OMS, the second (Dr. Pranzatelli) is the Joshua to Dr. Kinsbourne's Moses, while Dr. Cohen just has the occasional OMS patient. There is nothing in Dr. Cohen's career, writing, or research that would make his knowledge of OMS impressive.

Dr. Kinsbourne's testimony that DTaP can co-stimulate the immune effect of a neuroblastoma to cause OMS based on Dr. Pranzatelli's writings has satisfied the first prong of Althen, providing a plausible medical theory that the vaccine can cause OMS.

Dr. Kinsbourne's testimony that DTaP in this case logically caused, together with neuroblastoma, CHILD DOE 79's OMS has satisfied the second prong of Althen, proving a logical sequence of cause and effect. He has satisfied the Shyface requirement of proving that DTaP was a substantial factor, together with the substantial factor of the neuroblastoma, in causing CHILD DOE 79's OMS and that, without the DTaP, CHILD DOE 79 would not have had the OMS since it is not uncommon for neuroblastomas to regress and disappear without further immune stimulation but, unfortunately, the immunization provided further immune stimulation.

Dr. Kinsbourne's testimony that the month interval between DTaP and the onset of CHILD DOE 79's OMS is a medically appropriate time frame to manifest causation has satisfied the third prong of Althen, showing a temporal relationship between vaccination and illness.

Four years ago, the undersigned issued a decision on the same issue, involving MMR vaccine instead of DTaP, in Mulvaney v. Sec'y of HHS, No. 05-556V, 2006 WL 2438454 (Fed. Cl. Spec. Mstr. 2006), in which the child had a 15-day interval between vaccination and OMS and also had a neuroblastoma. The undersigned held, based on Dr. Kinsbourne's testimony and the articles and writings by Dr. Pranzatelli, that the MMR was a substantial factor as well as the neuroblastoma in causing the child's OMS. The testimony by both sides's experts was practically identical to their testimony in the instant action. The child in Mulvaney was also Dr. Pranzatelli's patient. Nothing has changed in four years to change the undersigned's opinion on the same issues in the instant action.

The medical literature which both sides filed in this case by various authors, not only Dr. Pranzatelli, repeatedly states that OMS is an autoimmune disease, and often describes children who had immunizations before the onset of their OMS. In respondent's Exhibit C (the Stefanowicz article), the authors analyzed the cases of four OMS children. The first two had preceding immunizations, and the third had a preceding infection. The authors were interested enough in the fact of immunization that they had a separate entry point in their table of data to reflect whether the case child had a previous immunization before diagnosis with OMS. None of the authors of this article was Dr. Pranzatelli. Unlike Dr. Cohen's dismissal of Dr. Pranzatelli's views about the immunologic effect of immunizations on children who later develop OMS, the

medical community does take seriously whether or not there is a history of immunization in an OMS child in addition to whether or not the child has a neuroblastoma.

Both parties filed the same article by Dr. Pranzatelli (petitioners' Exhibit 30; respondent's Exhibit E) in which he states: "Environmental factors are likely to be very important in OMS, including infecting agents such as viruses or bacteria and immunizations or vaccinations." The undersigned takes Dr. Pranzatelli's words seriously. Dr. Pranzatelli's reputation, his accomplishments, and his building upon the work started by Dr. Kinsbourne ground this case in scientific and medical credibility.

Petitioners have prevailed in proving that CHILD DOE 79's DTaP was a substantial factor in causing, together with her neuroblastoma, CHILD DOE 79's OMS.

CONCLUSION

Petitioners are entitled to reasonable compensation. The undersigned hopes the parties may reach an amicable settlement. A telephonic status conference will be set soon to discuss how the parties will proceed in resolving damages.

IT IS SO ORDERED.

July 20, 2010
DATE

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