Horner's Syndrome and Neuroblastoma: Our Family's Odyssey with Disorders of the Sympathetic Nervous System

September 11, 2010: the anniversary of a national tragedy and a date that changed our family forever. While at my son's soccer game, my wife, Stacey, realized something was not quite right with Paige, our 17 month old daughter. It was a scorcher of a day, and Paige began sweating and became flushed but only on the left side of her head. It was as if someone had drawn a line down the middle of her face and one side was bright red and the other pale. Stacey immediately told me that we have an issue with Paige's sympathetic nervous system and that she was presenting with what she thought was Horner's syndrome (*1*). What? You see, Stacey is in Physical Therapy School and a former medicinal chemist at Merck, and her Professor covered Horner's syndrome the day before in Neuroanatomy: this proved to a very fortunate timing of events and one that probably saved our daughter's life. Horner's syndrome, also referred to as Bernard−Horner syndrome or oculosympathetic palsy, is acquired by damage to or pressure on the sympathetic nervous system (*1*). The clinical features of Horner's syndrome include ptosis (drooping eyelid), anhidrosis (decreased sweating on the affected side of face), and miosis (constricted pupil) (*1*). On closer inspection of our daughter, both the ptosis and miosis were discernible as well. Looking back through photographs, we were able to identify that the miosis was present in photos from late June of 2010, but not before; therefore, the Horner's syndrome was relatively recent. While not life-threatening, we scrambled to find the cause and quickly ran through the list of known causes, ruling one out after the other and quickly finding ourselves facing unthinkable culprits.

We then rushed to the ER of the Vanderbilt Children's hospital. The attending physician was shocked that my wife had correctly diagnosed the Horner's syndrome, which is relatively rare in young children. Then, we heard what we had been fearing: the likely cause is a tumor pressing on her sympathetic nervous system. A chest X-ray identified an opaque mediastinal mass. Standard blood work provided no insight, because Paige's counts were all within normal range. Hours later, a computerized tomography (CT) scan definitively confirmed the presence of a tumor in the mediastinum. It is hard to know exactly what was happening, as we grappled to deal with the idea that our baby girl had a tumor, possibly cancer, but we were admitted to the hospital. Speculation based on location of the tumor and the impact on the sympathetic nervous system pointed to either a ganglioneuroma, a ganaglioneuroblastoma, or a neuroblastoma (*2*). The next week of tests seemed to last an eternity. Nine unsuccessful IV lines led the team to place a peripherally inserted central catheter (PICC) line for access for blood draws and to administer fluids and future chemotherapy.

The pediatric oncologist felt strongly from the beginning that we were dealing with a neuroblastoma, the second most common (10.5 million cases/year worldwide) extracranial malignant tumor in children (accounting for 50% of all cancers in children under two), which accounts for ∼10% of all childhood cancers and ∼15% of cancer deaths in children (*2*). Derived from progenitor cells of the sympathetic nervous system, neuroblastomas belong to the "small round blue cell" neoplasms of childhood (*2*). The oncologist advised us not to look online and read about neuroblastomas. My wife heeded the warning, but I did not, and I was not prepared for what I found. A number of histological and genetic factors, along with the presence or absence of neuroblastoma in glands and bones/bone marrow, differentiate the prognosis from >98+% survival to less than 30%. Age plays a major factor, with the most favorable prognosis being for children under 18 months of age and the prognosis worsening for each six month step thereafter. Fortunately, we had age on our side (*2*).

The formal diagnosis for neuroblastoma employs a combination of biochemical, histology, imaging, and staging steps. Paige next underwent a full body CT scan to determine whether there were other tumors that the chest CT might have missed, because neuroblastoma usually originates in adrenal glands. The scan was negative, and it appeared that we were dealing with a lone tumor. In ∼90% of neuroblastomas, elevated levels of catecholamines, such as homovanillic acid, **1** (HVA), and vanillylmanedlic acid, **2** (VMA), are found in the urine (*2*). Thus, a urine sample was taken, but this was an outsourced assay, and results would not be available for 3−5 days. The team then proceeded with a biopsy of the tumor, using arthroscopic surgery and also took a bone marrow biopsy to determine whether the cancer was in the bones or bone marrow, since this would significantly worsen the prognosis and require an arduous and painful treatment regimen. Stacey and I sat for hours while the biopsies were being performed, hoping for the best in a terrible situation. The surgeon finally came in and let us know that Paige did well during the procedures. The tumor was highly necrotic, and was outgrowing its blood supply. While he felt he could surgically resect the tumor, it was "soft" and he preferred to

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wait for chemotherapy to "toughen" it up. Late that night, we received preliminary word that the bone marrow was not involved! What a relief. Had the bone marrow been involved, treatment would require radiation, bone marrow transplants, and extensive chemotherapy. We now waited for the histology of the tumor.

The next morning, we were told that the histology was indicative of a malignant neuroblastoma (Schwannian-stroma poor). However, it was highly differentiated with a low (<1%) mitotic−karryorhectic index (MKI). Final bone marrow biopsy results were negative. Interestingly, when the urine analysis for HVA and VMA was returned, all levels were within normal ranges.

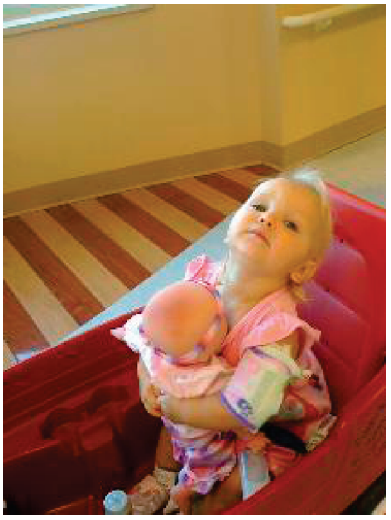

Figure 1. Paige in the Children's hospital after a week of tests.

These data placed Paige in a more favored prognostic category, but the one wild card we did not yet have in hand was the *MYCN* status, which would take about 3−4 days. While awaiting this data, the oncologist perfomed a single photon emission computed tomography (SPECT) imaging study to ensure that there was not any neuroblastoma that the CT scan missed. Approximately 95% of all neuroblastomas and sympathetic neurons selectively take up an ^{123}I-labeled *meta*-iodobenzylguanidine, **3** ([^{123}I]mIBG), or so-called mIBG scan (*2*). Once again, we were fortunate in that the mIBG scan was clean.

The last piece of the puzzle to assign a stage, and prognosis, to Paige's neuroblastoma was whether *MYCN* (also referred to as N-*myc*) was amplified. The *MYCN* oncogene is present in increased copy number in 25−30% of neuroblastomas and found amplified in ~40% of the high risk stage 3 and 4 neuroblastomas. *MYCN*-amplified nueroblastomas are highly aggressive and correlate to a poor prognosis (< 30% survival) (*2*). Once again, we received the best news possible: her neuroblastoma was *MYCN* negative, which allowed her neuroblastoma to be categorized as a stage II. While this was a tremendous relief, we were surprised at the treatment regimen and the fact that the chemotherapy had changed very little in the past 20 years. Paige would receive four cycles of chemotherapy based on her staging; however, our oncologist suggested a clinical trial where she would receive only two rounds of chemotherapy (cycle 1, carboplatin (**4**) and etoposide (**5**) (day 1), etoposide (**5**; day 2), etoposide **5** (day 3); cycle 2, carboplatin (**4**), cyclophosphamide (**6**), and doxorubicin (**7**) (day 1)), followed by a CT and surgical resection of the tumor. As

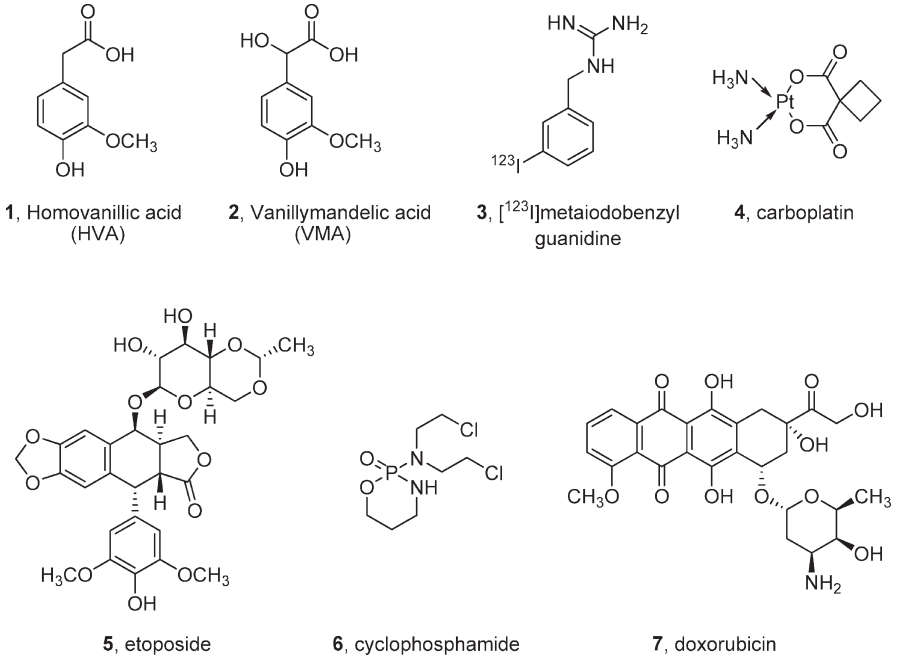

Figure 2. Structures of key compounds discussed in the text.

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a medicinal chemist, just looking at these structures and knowing they were being infused into my daughter broke my heart. How could this be the standard of care in 2010? Interestingly, in Japan and Europe, neuroblastomas are treated with surgical resection alone. Based on potential long-term health risks of prolonged chemotherapy in such a young child, we enrolled Paige in the trial. The next day, an article in the *New England Journal of Medicine* published trial data in higher risk neuroblastoma patients with reduced cycles of chemotherapy that provided equivalent survival and outcome to the standard, extended regimen (*3*).

At the time of this writing, we are about to begin cycle 2 of the chemotherapy, and Paige is handling everything wonderfully, far better than we expected: only one ER trip for a fever, which required IV antibiotics, during cycle 1, and the daily Neupogen, a biologic from Amgen used to treat neutropenia, injections to stimulate white blood cell protection was terminated early because her counts climbed faster than expected. Paige is a real hero, as are all children with pediatric cancer; throughout everything, Paige has kept her smile.

The Horner's syndrome proved to a blessing, because it allowed us to catch the cancer very early, providing a favorable prognosis. The more we learned about neuroblastoma and related childhood cancers of the sympathetic nervous system, it became alarmingly clear that more research is required to identify discrete molecular targets for therapeutic discovery and move away from the old, indiscriminant cytotoxic agents still used as frontline therapy. If the disease is not caught before 4 years of age, the prognosis is very poor. Surprisingly, the simple urine tests to detect the neuroblastoma metabolites **1** and **2** are not routine at standard check-ups for children under the age of 5. This alone could allow for early detection and more favorable outcomes. New advances are being made with microRNA, but this is an area where children, parents, and pediatric oncologists are truly waiting for an advance. Neuroblastoma is interesting in that it is both a CNS disorder and a malignant cancer. This is the perfect arena for neuroscientists and oncologist to work together toward redefining the standard of care and addressing a serious unmet medical need.

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