# Beckwith-Wiedemann Syndrome: Partnership in the Diagnostic Journey of a Rare Disorder

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Conditions like Beckwith-Wiedemann syndrome (BWS) carry a risk of an associated aggressive malignancy, and thus timely diagnosis is critical. Without a clear diagnosis and timely, appropriate medical care, complications of BWS-associated malignant tumors can be life-threatening or require organ transplant that otherwise could be avoided. Diagnosing rare pediatric syndromes remains challenging. Often the diagnosis may be aided by an astute pediatrician or a parent recognizing a subtle feature related to the syndrome. This establishes a valuable partnership between pediatrician, parent, and geneticist that can lead to a diagnosis. Without this partnership, families may embark on a diagnostic odyssey for years while their child remains at risk. We share the perspectives of 2 parents and a geneticist in an effort to raise awareness and promote early diagnosis of 1 of many rare diseases.

Classically, BWS is an overgrowth and cancer predisposition disorder for which several clinical diagnostic algorithms have been developed.[1] Diagnosis may be difficult when a child has only 1 feature of the syndrome (eg, macroglossia) or 1 or more less commonly known features. A pediatrician who is unfamiliar with the variability in the presentation of BWS may dismiss the diagnosis. Parents have access to a wealth of information on the Internet, and this access may enable them to identify subtle features. Pediatricians must be open to the parents' considerations. The cases described below highlight the importance of access to information for both parents and physicians and the role that parents can take in contributing to the partnership with health care professionals. There are many pediatricians, both generalists and specialists, who create a partnership such as we describe in the article that follows.

## JENNIFER KALISH, MD, PHD, PEDIATRIC GENETICIST

The doctor–patient relationship has evolved from the pedagogical and hierarchical model to a partnership. Within that partnership, especially in the case of rare diseases first seen by general pediatricians, parents often find themselves in the disconcerting position of being the most well-versed party in the clinic room.[2] This dynamic is because of a combination of accessible knowledge for motivated parents and the growing number of disorders that do not fit the textbook mold physicians encounter in training. Pediatrics is such a broad specialty that even the most well-informed generalists and specialists cannot keep up with every nuance and breakthrough. However, in addition to lifelong learning, access to the most up-to-date information, and consultation with other specialists, partnerships with patient families allow us to broaden our understanding, which leads to the diagnosis of these rare diseases and appropriate ongoing care.

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In medical school, BWS is barely mentioned. Students may be asked a question related to classic features, such as, "A large child with macroglossia: What is recommended?" BWS is presented as rare, about 1 in 10 500 patients.[3] The actual incidence is likely higher because of the range of more subtle presentations and the increased risk associated with in vitro fertilization[3–5]; both facts are not currently in textbooks, and had just been introduced into the medical literature when these patients first came to my clinic. The rapidly evolving knowledge about rare syndromes represents a challenge for physicians and demonstrates the importance of both continuing medical education and of partnering with parents who may walk into the office with the data needed to reach a diagnosis.[2]

## ALISHA DAVLIN, PARENT

It took a bit over 2 months to get my daughter, Ary, diagnosed with BWS. She only had 1 obvious feature: macroglossia. Yet, she did have 3 of the "classic BWS" stork bites, and I had what my Obstetrician-Gynecologist called the longest umbilical cord he had seen, which are all BWS details that I had discovered online.[6] Ary could not close her mouth because of her enlarged tongue. We saw 4 different pediatricians, each of whom informed us that she would close her mouth when she grew teeth, or that "babies often stick out their tongues." Interestingly, no one inquired about whether she was conceived through in vitro fertilization. No one entertained my armchair diagnosis of BWS. Finally, after reading that syndromes can present with subtle features, the last pediatrician sent us to a geneticist for further evaluation. Originally, as is the case for many parents, the wait to see a geneticist was months. However, I persisted, explaining that the possible diagnosis of BWS carried a cancer risk, and thus, my daughter needed to be seen as soon as possible (an important point for the pediatrician to make during the referral process). We were seen within a few weeks. There, the geneticist provided a clinical diagnosis of BWS and quickly explained the cancer-screening protocol to us. We were also handed a few sheets of information printed from the Internet, which I later learned was outdated. One statistic sent my heart plummeting: "1 in 5 babies dies."[7] We needed more guidance. We searched local hospitals but no one had ever heard of the syndrome. I had so many questions and fears. We found Dr Kalish a few weeks later.

## DR KALISH

My interest in BWS started with 1 patient who did not resemble the textbook cases. Her only clinical feature related to BWS was hemihypertrophy. Her parents asked, "Why is she at risk for developing tumors?" Like many other new parents, they came with pages of Internet research, which discussed the classic features, such as macroglossia and omphalocele. Their daughter had neither of these features. "Does she have BWS?" These questions presented me with my own personal questions: How do we, as physicians, take the medical knowledge in books, medical journals, and the Internet, and translate it so it applies to the patient and family, transforming perception into diagnosis and management? My patient's parents continued: "What is her tumor risk? Why are physicians unsure of her diagnosis?" As physicians, we learn that there are zebras, and there are horses, but it turns out that there are hybrids or mosaics: part zebra, part horse, and those are much harder to diagnose and understand. Since this patient and her family, we have seen many other patients who have BWS but did not meet the current BWS criteria.[3]

## ALISHA

As parents, we realized that even with wonderful doctors, there exists a need to develop a comprehensive partnership in both diagnosis and care. This partnership serves to educate parents and our physicians, many of whom have no experience with BWS. When our daughter was first diagnosed with BWS, we had numerous questions and needed both peers, other parents in similar situations, and reliable resources to address and answer our questions. What we wanted most in that early period after the diagnosis was someone to help coordinate our child's care, someone to help us digest the word "syndrome," which feels so frightening to a new parent. We needed a contact person to guide us to the other specialists: a plastic surgeon for macroglossia, an orthopedic surgeon regarding her leg length discrepancy, as well as feeding and speech specialists, and to partner with our primary pediatrician.

When we first met Dr Kalish in the clinic, my husband, who is a scientist, was prepared with many questions. First and foremost on our mind was the 1 in 5 death statistic that had devastated us. Dr Kalish told us that number was outdated and gave us a detailed understanding of our daughter's epigenetic change and its effects. Despite learning so much about BWS at that visit, we were left with many questions that Dr Kalish could not answer: "What will Ary's legs look like as a teenager?" and "Do you have any pictures of a 14-year-old patient with BWS?" To each of these long-term questions, she replied, "We don't have enough data." No repository of photos of patients with BWS existed, but she stated that she was starting a registry to manage these children throughout

their lives. In that moment, we realized that having a resource was not enough, we needed to work with Dr Kalish to develop more resources such as the BWS registry to advance BWS research both to help our daughter and other families and to provide information to physicians as well.

### CATHERINE CLARKIN, PARENT

We first met with Dr Kalish in 2015 when my son James was 11 years old. Because James is one of her oldest patients, and little research has been done on adolescents and teenagers with BWS to date, many of our questions remain unanswered. Looking forward, some things are known. He will have a surgery to stop the growth in his longer leg at the time the orthopedist estimates his other leg will be able to catch up before he stops growing. If James chooses to have children, they will not be at elevated risk because he has a noninherited subtype of BWS. Other concerns are less well understood. Will his kidney issues worsen? Should he continue to be monitored because of liver and pancreatic cysts? Does his enlarged testicle put him at higher risk for cancer? Will BWS and all the medical visits have a negative emotional impact?

### DR KALISH

Over the past few years, we have developed some answers and many more questions. "Why do many children with BWS not look like the textbook?" The short answer is because we have recently discovered that the (epi)genetic changes are actually mosaic, meaning that the changes occur in some cells and not in other cells, in most cases of BWS. This mosaicism leads to both the variety of clinical features with which patients with BWS present and a limitation in genetic testing, in which the test is only positive if the genetic change occurred in the sample tested. This creates challenges to the diagnostic approach because the diagnosis is still primarily based on clinical criteria and those criteria can be variable. Furthermore, a diagnosis cannot be excluded in the context of negative genetic testing because of this mosaicism. These considerations have led to an international effort that is currently underway to develop BWS diagnostic and management consensus guidelines.

Approximately 30% of our clinical cohort has the classic, textbook features of BWS. The remaining patients have more subtle features, such as isolated hemihypertrophy. As specialists we need to partner with families and pediatricians to gather clinical data and questions and work together to improve understanding of BWS. Through the registry we have been able to start studying this spectrum in clinical presentation with the hope of beginning to answer the questions that so many parents have. BWS is just 1 example of many disorders in which a partnership between the parent, the patient, and the physician can lead to a much-needed diagnosis.

### ALISHA

The most important aspect for me as the parent of a child with BWS is to find ways to help physicians and other parents find answers to the many questions we have for our children. To do that, I have teamed up with Dr Kalish and encouraged other parents to do so as well to support the BWS registry both through sharing my daughter's clinical information, but also by asking questions about BWS. Often, I will come to Dr Kalish with a question raised by my online BWS support group and she will add that question to the registry research. "Is there an autism connection to BWS? Are there behavioral issues?" Or more mundane ones: "How much should I feed my child?" Because BWS is an overgrowth disorder, I struggled the first year knowing how much to feed Ary. We saw a few nutritionists, but none had experience with children who have BWS, and thus could only supply standard health recommendations. Through the registry data, we have helpful suggestions and these questions turned into research categories for the registry. Thus, not all of our questions were strictly medical; we required a specialist with a holistic approach to dealing with the idiosyncrasies of this syndrome and help to formula a plan to collect the necessary data to address these questions. And it can be hard to separate first-time parenting struggles from syndrome-related issues when it comes to an orphan disease.

### CATHERINE

As a parent of a child with a cancer-predisposition syndrome such as BWS, you find yourself wondering if every pain or illness is the first sign of cancer. Worries can overwhelm, no matter how knowledgeable we are, so, partnership with trusted physicians and other families with similar experiences is critical for the health of our son as well as our own mental health. The more we and James' doctors can understand BWS, the better care James will receive and the more confident we will feel about his care.

### ALISHA

My partnership with Dr Kalish has become truly collaborative. My family has helped to raise awareness for the BWS registry and encouraged other families to join and share their questions, especially in our Facebook support group. The BWS registry has become a resource for the larger BWS community, both in answering questions and in connecting families

together with similar concerns and questions. Whenever I come across an outdated BWS Web site, I send it to the registry and they will help update the major Web sites that parents will come across on the Internet.

### CATHERINE

Being part of the BWS Facebook community and the BWS registry has been educational and has also allowed me to give back to the community. It was through the BWS Facebook group that I learned about Dr Kalish and the registry. I was eager to have James become part of the BWS registry so that our experience can benefit others. I remember in particular, a parent whose infant had an adrenal mass who had been told before surgery that it was definitely cancer. Based on our experience in the same situation, I was able to reassure her that kids with BWS can also have benign growths and so there was reason to be hopeful. It did turn out that her daughter had a benign adrenal adenoma, just like James. Her doctors also learned that BWS does not always equal cancer.

### DR KALISH

In the past few years, we have updated outdated information and developed the BWS registry, which demonstrates the true partnership approach between clinicians, researchers, and families to develop ways to answer our questions. Our goal is to achieve more awareness that will lead to an early diagnosis because children with BWS are at risk for hypoglycemia at birth and tumors during childhood and require proper treatment and monitoring.

### ALISHA

I am deeply satisfied that the 1 in 5 statistic will not be seen by a new frightened parent. That said, there is still more work to be done. With the BWS registry, our hope is that future parents will not hear "there's not enough data." They will ask and their questions will be answered. The BWS registry will help parents concentrate on raising their children instead of anguishing over every possible BWS manifestation because of all the unknowns. It will allow kids to be kids and parents to be parents and to work with the experts to collect the much-needed data.

### CATHERINE

So little research has been done on patients with BWS once they reach puberty and beyond. My hope is that the BWS registry will help older patients better understand their medical risks and how to manage their health.

### DR KALISH

Since BWS was first characterized over 50 years ago, we have developed a better understanding of the range of clinical features and how to manage some of these features, but many unknowns remain. We are fortunate that in the age of social media and information access, we can now partner with families, connect families to each other, and work with pediatricians to improve our ability to diagnose, manage, and systematically address these many unknowns. These partnerships are invaluable to understanding the nuances of rare diseases and helping patients and their families live the best lives possible. I recognize that I am but one of many pediatricians who strive to create such partnerships with the families they care for.

### ABBREVIATION

BWS: Beckwith-Wiedemann syndrome

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