

Will the “Real” Joubert Syndrome please stand up? One geneticist’s perspective

I have now attended three Joubert Syndrome Foundation and Related Cerebellar Disorders conferences, and each time I have enjoyed meeting so many wonderful children and their families. You all are the reason we do what we do. Sometimes I hear comments from parents who feel perplexed, confused, and even angry that scientists can’t seem to agree what Joubert syndrome really is, and even worse, may suggest that some of their children might not have Joubert syndrome at all. Instead, they may have some other scary and poorly-defined condition that is even harder to spell and pronounce than Joubert syndrome! I can understand why some parents would have that response, and I wanted to share some thoughts from the medical perspective that may be helpful. We as medical providers have been working through some of the natural growing pains that occur in struggling to understand a relatively new condition. Let me give you some background on how this process works.

As a representative of the scientific community, let me explain that first of all, we greatly regret if we have implied that your child doesn’t belong in the Joubert syndrome category or community. That is certainly not our goal. In fact, now that the Joubert Syndrome Foundation has expanded to include “Related Cerebellar Disorders,” all parents with a child with a brain difference involving the cerebellum should feel that they have a home within the JSF&RCD.

Some background on how medical geneticists classify: “lumping” vs. “splitting”

Joubert syndrome is still a very new condition, since it was first described in 1969 by Dr. Marie Joubert and colleagues. This means that we have had a relatively short period of time to start to understand what “Joubert syndrome” really means. The molar tooth sign was first described in 1997 by Dr. Bernard Maria, and we have had less than 10 years to use this as a tool to aid in diagnosis. Within the past 15 years, the resolution of MRI scans of the brain has also dramatically improved, and is likely to continue to improve. As happens so often in the medical field, and in particular, genetics, when a new condition is first described, there is a flurry of attempts to use the new diagnosis to help characterize children who have not previously had a helpful diagnosis. This is the process known as “lumping,” which means that many children with cerebellar hypoplasia and some other key features (such as eye abnormalities, breathing problems, developmental delays, and low muscle tone) may be given this diagnosis to “try on for size”. It’s like seeing if a brand new winter coat fits, and although many different people with different body shapes could wear the same coat, it may not be a perfect fit for everybody.

This is where “splitting” comes in. Often, as we start to learn more about the children who have been given this diagnosis, we realize that there are differences in their medical problems, development, behaviors, and long-term health concerns. In genetics, we try to look for useful patterns that help us identify subcategories for certain conditions. These subcategories are only useful when they provide diagnostic, prognostic, or management predictions. In other words, subdividing (or “splitting”) just for the sake of splitting is NOT useful. To continue with the coat analogy, whether a coat is red or blue should not make a difference as to how well it fits a given person. However, a heavy down coat is going to fit a person better who lives in a cold climate, whereas a light jacket may be a better fit for a person from Arizona.

A spectrum of Joubert syndrome: Joubert Syndrome and Related Disorders (JSRD)

When splitting occurs, scientists often bring in new conditions that have different, unfamiliar names, and ask if they should also be included in the subdivision process. That’s why some families may have heard terms such as “Dekaban-Arima,” “Senior-Løken,” “Varadi-Papp,” “Cogan-type Oculomotor Apraxia,” and “COACH” syndrome mentioned in addition to Joubert syndrome. These names may not seem helpful for families at first, and the medical practice of using proper names or abbreviations to describe conditions is indeed confusing, even for doctors. However, these names may be useful to us scientists in looking through the medical literature,

because these terms can help us learn about children who have been described in the past and in this way, we can share information more effectively with each other. These labels may also reflect the way specialists in different medical fields emphasize specific clinical features in the patients they see in their practice, and the shared nomenclature among a group of specialists is very valuable for their communication.

I think one of the most useful conclusions among researchers is that what is termed “Joubert syndrome” represents a spectrum of disorders that have some features in common but other features that vary. This may sound obvious to many of you who have been attending the Joubert Syndrome Foundation conferences for years, because you know that your child is similar to some of the other children with Joubert syndrome, but is also very different from other children. How we understand and categorize those similarities and differences is the real challenge. One area of consensus is that the fundamental feature of the “molar tooth sign” visualized on specific views of an MRI scan is a critical step in making a diagnosis of Joubert syndrome. Other features, such as kidney problems, eye or retinal changes, and liver problems, are likely to be specific to certain subgroups of Joubert syndrome. We call these “Joubert syndrome and related disorders” (JSRD), and we now agree that these conditions have, at the minimum, the molar tooth sign in common. Thus, conditions such as Senior-Løken syndrome and COACH syndrome really are part of the spectrum of what we now consider JSRD. It should be remembered that children with other rare brain malformations that have not been considered “classic” for Joubert syndrome in the past (such as Varadi-Papp syndrome) may have a molar tooth sign, and they may now be considered a part of this family of conditions.

Nobody likes labels, but they provide useful information. Although using difficult eponyms such as Dekaban-Arima syndrome or Senior-Løken syndrome can be confusing for parents and most physicians, it may be the best option thus far. How, then, should we describe the different subtypes of Joubert syndrome in the future? Borrowing from the medical literature, one type of terminology that might be used is numbers, for example “Joubert syndrome-type 1” or “Joubert syndrome-type 2.” This would require defining the specific features of JS-1 and agreeing upon them, which is not easy. Alternatively, since we know that more than one gene causes Joubert syndrome, we may use “*NPHP1*-related Joubert syndrome” to describe children who have a genetic change in the *NPHP1* gene, and “*AHI1*-related Joubert syndrome” to describe those who have a change in the *AHI1* gene, and so on. As you can see, this logical form of classification requires the discovery of the Joubert syndrome genes, a difficult task that we are actively pursuing.

The importance of an accurate diagnosis: different genes, different outcomes?

You might wonder why the subcategories are so important, if it's all just Joubert syndrome anyway. This is why it is crucial: A child with Joubert syndrome due to deletions in the *NPHP1* gene, for example, may be more likely to develop kidney problems than a child with Joubert syndrome due to *AHI1* mutations. If we know that a specific type of genetic change is never associated with kidney problems, we can tell a family that the risks of kidney failure are almost zero (geneticists never say “never”!). If I were a parent of a child with JSRD, I would want to know this information. An accurate diagnosis, whatever nomenclature is agreed upon, allows for more accurate information so that parents, physicians, and therapists can provide the best possible care for each individual child. This is also why genetic studies and a national Registry are so important in Joubert syndrome and why your participation is crucial. The more families who participate in providing clinical information and donating blood samples, the more likely we will be to identify the genes that cause this spectrum of conditions, and the better diagnostic and medical information we can give you. In my experience as a geneticist, many, many conditions have different clinical profiles depending on which gene is causative, although they may look confusingly similar before the genes are discovered. Only with the discovery of causative genes do some of these differences become understandable. Although we can't guarantee that this will be the case for Joubert syndrome, there is some emerging evidence that different symptoms and medical problems may be more likely to be caused by different Joubert syndrome-related genes.

However, there will always be many common medical problems for all Joubert patients, which makes it sensible to retain a common support group, i.e., “strength in numbers.”

A dynamic partnership between parents and medical professionals is essential

As a geneticist, I spend a lot of time with families trying to give them the most accurate and specific diagnostic information available. But I recognize that the field of genetics is constantly changing, and new information is always being discovered. Even when I make a specific diagnosis for a child and am able to provide a genetic test that confirms this diagnosis, I always tell parents to stay in touch periodically, and I generally recommend a follow up appointment in 1, 3, or 5 years. This is to provide new information that we hope will be helpful for them. As research unfolds, I anticipate an explosion of new information about Joubert syndrome that will continue in the next several years.

Here’s where parents can help. The new information and medical literature that we rely on for information about rare conditions such as Joubert syndrome comes from only one ultimate source: you! In addition to blood samples to help with genetic linkage studies, we need your input about how your child is doing, what observations you have made, copies of clinical reports, and the results of a variety of tests such as renal ultrasounds, eye exams, and blood and urine tests for kidney and liver function in order to understand the similarities and differences between children with Joubert syndrome. This is why your participation in a national Registry is so vital. This is why we keep asking you to answer questions about your child over and over again. The questions we ask today are much more sophisticated than the questions we asked even 5 years ago! So please help in the partnership to understand this condition by sharing your wisdom about your children.

Some important conclusions

Since we can’t yet perfectly sub-classify children with Joubert syndrome on genetic and/or clinical features yet, we have to be cautious about long-term risks for complications such as vision, kidney, or liver problems. As a result, annual evaluation recommendations for children with Joubert syndrome have been established with guidelines for MRI testing, vision, kidney and liver function, developmental and behavioral testing. These recommendations can be found on the Joubert Syndrome Foundation and Related Cerebellar Disorders website at www.jsfrcd.org under the “Evaluation Recommendations” link.

Final thoughts: A diagnosis doesn’t change who your child is

In my genetics practice, sometimes I have to tell parents that the diagnosis they were given years ago based on incomplete information (or the best information available at the time) isn’t the best diagnosis for their child today. This can be very difficult for many parents, because as much as we hate labels, they also provide a handle to understanding, an identity, and the support of others who share the same challenges. I always try to provide information on support groups for such parents. More than once, I have told parents that even if a particular diagnosis isn’t the “best fit” for their child, if they derive benefit from being in a particular support group, by all means, keep participating!! You have a dynamic, proactive, and compassionate group of members and current officers in the Joubert Syndrome Foundation and Related Cerebellar Disorders group, and I hope you continue your involvement with this wonderful organization, no matter what JSRD or cerebellar condition your child has. As you all know, a specific diagnostic label doesn’t change anything about who your child is. All of the children (and adults) I meet at the Joubert syndrome conferences are special, unique, and wonderful human beings.

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