May 2020 Virtual Family Event: Question & Answer

In order to protect the privacy of all community members who joined the family event on May 1, we have scribed the question and answer portion in lieu of publishing any video or audio. Please note that the answers to the below questions are general recommendations for the Kabuki syndrome community and are not to be used as specific medical advice for any individual. If you would like to review any information in further detail, or have additional questions that are not answered below, please feel free to reach out to kabuki@childrens.harvard.edu and your question will be directed to appropriate Roya Kabuki team member for response.

OB: Olaf Bodamer, MD, PhD
BG: Benjamin Goodlett, PhD

1. Why does the left side seem to have more issues?
   OB: Interesting question. When we look at the heart in Kabuki syndrome the left sided structures are most commonly affected. This has to do with the way the heart develops during the first few weeks of embryonic development, which is a very complex process. The heart develops in an asymmetric fashion, and the underlying genetic problem in Kabuki syndrome affects those genes that play an important role in the development of the aorta, left ventricle, and left sided heart valves. Other than the heart, I have not heard any additional arguments that would speak to why the left side is more heavily affected. I have not seen a child with asymmetric growth of the left body side compared to the right body side. I have not observed, for example thinking about the kidneys, that the left kidney has been more affected than the right kidney. Kabuki syndrome has been seen to affect organ systems in an equal distribution.

2. Do I need to be concerned of potential heart issues if we haven't had any to this point?
   OB: We do not see any reason for increased risk for arrhythmias or other potential heart concerns provided the child did not have any cardiac concerns from birth. There are no concerns for new structural anomalies of the heart as the child develops.

3. Several parents reported their child's liver enzymes are high, but bilirubin is only slightly elevated. Is there any research being done on this?
   OB: We observe a number of children and young adults who have an elevation of liver enzymes, sometimes elevation of an enzyme called alkaline phosphatase, and less so of bilirubin. Elevation of liver enzymes points to a direct toxicity in liver cells and there are many different reasons why this could occur. In otherwise healthy children, this might occur due to exposure to medication that affects liver metabolism.

   We also see trend to this in children with an auto-immune disease or immune deficiencies, and I think that is the likely connection with KS. Auto-immune disease occurs at a higher frequency in those with Kabuki syndrome, and immune deficiencies can affect the ability of the liver to function normally. This may create a situation where the organ starts to develop antibodies against either the liver cell itself or components of the liver cell, which in turn might affect the liver cells ability to function normally. The result we see at the laboratory testing level is an increase in liver enzymes. When the cells of the liver are affected resulting in an elevation of bilirubin it does not typically extend to the small bile ducts, bile production, or the gallbladder.

There is research going on in other laboratories to better understand whether there is a correlation between the underlying genetic defect (genotype) and the extent of the effect on the liver. There is also some research going on that looks at the correlation of the extent of severity of immune deficiency and the involvement of the liver.

4. Do children with Kabuki syndrome who need a liver transplant seem to have more complications with transplant rejection?
   OB: When a child needs to have a liver transplant, in order to prevent the rejection, the child's immune system needs to be modulated with chemicals that compromise or lower immune response. This is essentially to prevent rejection of the transplant. If a child already has a significant immune deficiency this might interfere with the chemical treatment that is used to reduce transplant rejection and may actually cause an opposite reaction. We have seen this in other unrelated conditions when children are transplanted with an unrelated immune deficiency.

5. If genetic testing reveals a mutation that is linked with a specific syndrome (e.g. a mutation in KMT2D that is known to be related to Kabuki syndrome) why could this mutation be considered to be a VOUS?
   OB: This speaks to the interpretation and classification of genetic misspellings by the genetic testing laboratory. One way to think of this is that we all can carry genetic misspellings that might not actually do any harm. We would call these 'benign variants', or misspellings that do not results in any genetic condition. Because they don't result in any symptoms or related conditions, these would be chance findings. We all carry those benign variants.

   On the other hand, a variant or misspelling might be interpreted as a disease-causing variant, or a pathogenic mutation, if the laboratory knows that this misspelling causes a condition like Kabuki syndrome. This would mean that there is either evidence to support this interpretation because there are multiple patients with the same variation and the same or similar presentation of symptoms that are seen or observed in KS, or there is enough evidence for the testing laboratory to suggest that the functional result of that misspelling truly causes the symptoms we observe in the child.

   Sometimes we find a variation where there is no additional information. The genetic testing laboratory is faced with a variation they have never observed before and/or there is limited to no data available to support a functional impact. The laboratory will not be able to report whether this genetic 'misspelling' is actually disease causing or if it is benign. They call this a' variant of uncertain significance' (abbreviated VUS or VOUS). The lab is essentially uncertain of the significance of that variation as it relates to Kabuki syndrome.

   This question arises frequently when we test individuals who have symptoms that lead clinicians to believe there is a case to be made for a Kabuki syndrome diagnosis. If we order testing and see there is a variant in the KMT2D/KDM6A gene, we might be tempted to say that Kabuki syndrome is the explanation. In reality, if that variation has never been observed before and we don't have scientific evidence to support the functional impact we would still classify this as a 'variant of uncertain significance'. It is important to remember that these variants of uncertain significance are non-diagnostic. We cannot give that individual a genetically confirmed diagnosis of Kabuki syndrome. However, a clinical diagnosis of Kabuki syndrome based on symptoms might still be justifiable.

6. When we enter the Roya Kabuki program webpage it says, 'find a cure for Kabuki syndrome.' We would like to know what research you are doing, medication tests, and if there is a possibility to register to participate?
   OB: We view the statement to 'find a cure for Kabuki syndrome' as our moonshot, setting an extremely high bar for ourselves. We can only be as good as the bar we raise, and we aim to keep stretching until we reach that bar. It is our motivation every day, even during the pandemic.

   There are several research paths we are taking in the laboratory and the clinic to support this goal. One of which is completing the natural history study that provides us with information about the severity and variability of organ development in Kabuki syndrome, and also provides a timeline as to when we can expect certain symptoms to present and evolve as children and adults get older. This is an important pre-requisite for clinical trial. If a drug is identified that we feel has some efficacy (the ability to produce our desired outcome), we would have to test this drug in a formal clinical trial. We would have to know before the trial begins in which organ system(s) we expect efficacy, or effectiveness, of this drug.

   For example, there are concerns around Kabuki syndrome and neurodevelopmental delays. If we feel that drug 'x' has efficacy to improve neurodevelopmental delays, we have to identify which domain in the neurodevelopmental space is amenable and can be tested in a reliable manner over a relatively short period of time. We would then use this domain as an end point in a clinical trial. The last thing we want to do is test a drug that could have a potential positive outcome in patients, only to fail the clinical trial because we haven't given enough thought to the specific endpoints we are hoping to achieve. The natural history study will help us identify these potential domains and desired endpoints.

   Dr. Emanuela Gussoni focuses on better understanding the muscle involvement in children with Kabuki syndrome. We have research ongoing to understand the underlying mechanism related to why there is such a variability in severity and number of organ systems involved. We are also studying using KMT2D and KDM6A cell lines (from collected research samples) to understand whether there are medications currently on the market, or chemical compounds available, that could 'fix' certain Kabuki syndrome related changes at a cellular level. Once these medications or chemical compounds have been identified and tested at a cellular level, they can be moved to be tested on animal models with Kabuki syndrome before ultimately moving to clinical trial.

5. Could you also tell us which food supplements are suitable for Kabuki kids?
   OB: We recommend a healthy mixed diet. We always tell everyone to eat lots of vegetables and fruits, but food also has to be enjoyable. The occasional junk food or fast food can be tolerated. This question might be aiming at 'would we recommend the ketone bodies or other food supplements?' At the moment the word is still out on this. There is some scientific evidence to support the potential benefit of supplementation with ketone bodies. The ketogenic diet maybe beneficial, however we do not have the data yet in individual patients to fully recommend this diet. There are other food supplements such as creatine or carnitine that support mitochondrial production in an unspecific manner. Again, there is no scientific evidence to support such supplementation in children with Kabuki syndrome.

6. Many children with Kabuki enjoy music. Has anybody taken advantage of music therapy and get benefits from it?

BG: I certainly think this is a reasonable option to pursue, there is no reason why it would be a bad thing for children with Kabuki syndrome. If there are any families in the Boston Children's Hospital area, there are community partners that offer music therapy for teenage patients with genetic disorders. In my clinic I do know of a family that uses music therapy and the child gets a lot out of it. I think that with any type of therapy it is best to always keep in mind 'what are the goals?'. Is the goal to have a fun activity and to socialize, or possibly to help with behavioral problems and anxiety? It is helpful to have everybody on the same page about what the goal of music therapy is.

7. Should we be concerned about epilepsy? Is there is an age that this might develop by?
   OB: Epilepsy, in our experience and in the literature, occurs in about 20-30% of children with Kabuki syndrome. It typically starts with febrile seizures, meaning when a child has an acute illness and related temperature that causes a seizure event. With KS the threshold for having a febrile seizure is lower than we would typically expect. This can then either develop into an epilepsy that is more chronic and needs to be treated with anti-epileptic medications, or it can reoccur as a febrile seizure syndrome where there is an increases susceptibility for febrile seizures as the child gets older.

   One recommendation is to be more vigilant with fever and think about treating fever a little bit earlier than you might typically do in a healthy child. Most children who eventually develop a seizure disorder do so between the ages of 3-6 years. Obviously, there are some exceptions to that rule. For example, during early puberty there is a second risk however this is much lower than in early childhood. Epilepsy is typically well treated with anti-epileptic medications and needs to be followed by a neurologist. There is nothing particular or peculiar about the seizures in children with KS compared to an otherwise healthy child.

8. What is the indication for Growth Hormone?
   OB: The traditional indication for Growth Hormone (GH) is short stature. In Kabuki syndrome, in addition to stature, GH can also help with hypotonia. It will increase protein synthesis and lead to increased muscle strength and improved muscle tone and will therefore indirectly improve mobility of joints. Many children are hypermobile in their joints (both smaller and larger) and GH might also help with that aspect of the condition. There is good literature now from Europe supporting the benefits of GH, therefore it is something to be considered in patients with related symptoms. This is not a general recommendation and needs to be discussed on a case by case basis.

9. If there is a referral to endocrinology for consultation for growth hormone, are there any concerns or recommendations for parents going into that appointment?
   OB: The endocrinologist needs to have information about what the concern or indication for growth hormone is, which we know can be different in children with Kabuki syndrome than the typical population. We have received push back in the past if an endocrinologist takes the stand that the child is not growth hormone deficient. An endocrinologist would have to understand the additional benefits with GH for KS as explained above.

10. Is immunodeficiency more often associated with viral or bacterial infections?
    OB: This depends on which type of deficiency a child might have. The type of immune deficiency associated with KS is actually relevant for both viral and bacterial. There is likely an increased risk for mucosal bacterial infections such as otitis media and certain skin infections. There is an

increased risk for viral infections that are typically fought by immunoglobulins, so if you have a child with significantly low immunoglobulin levels who is not on supplementation there would likely be an increased risk for viral infection. Children who are on regular supplementation should do well.

11. Is it necessary to receive vaccines against the flu, and vaccinations in general, in children with KS?
    OB: I always feel that this is an important consideration. We typically recommend any vaccination. With the exception of the flu vaccine, we generally test all children with Kabuki syndrome for vaccination response to ensure that their response, or increase in antibodies, is sufficient. If not, these children might require a booster vaccination.

    With patients who are on subcutaneous IVIG, it is probably safe to assume that the IVIG that is used for the treatment will provide *some* immunity against flu viruses, for example. But you also have to consider that unfortunately the flu virus mutates, or changes, every year. This change is the reason that we need to receive a new vaccine each year. The IVIG might not provide enough immunity against a novel (new) flu virus.

12. Is Evan's syndrome common in Kabuki syndrome?
    OB: I have seen Evan's syndrome three times and have heard from colleagues in Europe that this is an emerging symptom in Kabuki syndrome. It is still fairly rare and generally seems to occur in children who have a more significant immune deficiency. This is still subject to future research.

13. Is there any indication for atypical female puberty?
    OB: Late female puberty, or delay in onset of puberty can occur in females with Kabuki syndrome. This can be associated with irregular menses or dysmenorrhea. One important aspect that seems to be associated with onset of puberty, in females more so than males, is a significant increase in weight gain. There are some potential underlying mechanisms in KS that would explain that.

14. Is short bowel syndrome seen in Kabuki syndrome?
    OB: We have 1-2 patients at BCH with Short bowel syndrome. Please feel free to reach out if you have specific questions and would like to discuss further.

15. What percentage of children in the Kabuki syndrome community have AHDH?
    BG: There are few articles on the percentage of patient in the Kabuki syndrome population with ADHD (attention deficit hyperactivity disorder). If we think of the core feature of ADHD being deficits in executive functioning (e.g. the ability to monitor progress on a task, ability to switch between tasks, ability to update memory on things that are going on right now, planning ahead of time, amongst others), those deficits are going to be things that are commonly difficult in children with KS.

    If a family with a child with KS came to me and said, ‘we have concerns for ADHD’, my initial response would be that this makes sense because there is a good chance that executive functioning has been impacted. For that child, ADHD as a question is certainly worthwhile. It would then be specific to each child about whether or not that is an appropriate diagnosis.