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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Understanding and Treating Birt-Hogg-Dubé Syndrome

DIAGNOSIS AND TREATMENT OF BIRT-HOGG-DUBE SYNDROME

Birt-Hogg-Dube syndrome affects a very small number of patients. What are we doing to diagnose and treat them? Welcome to The Clinicians Roundtable on ReachMD, the Channel For Medical Professionals. I am your host, Dr. Bruce Bloom and joining us to discuss the diagnosis and treatment of this orphan disease, Birt-Hogg-Dube syndrome are Mr. John Solly, Charity manager of the Myrovlytis Trust in the United Kingdom, a not-for-profit organization dedicated to finding secured for rare diseases and Mr. Eamonn Maher, professor of Medical Genetics at the University of Birmingham in the UK. Dr. Maher research is on the molecular basis of inherited developmental and cancer susceptibility disorders and coding for Birth-Hogg-Dube syndrome and he is the head of the Cancer Research UK Renal Molecular Oncology Group.

DR. BRUCE BLOOM:

Gentleman, welcome to ReachMD.

DR. JOHN SOLLY:

Hi, goodness to be here.

DR. EAMONN MAHER:

Thanks for inviting us.

DR. BRUCE BLOOM:

Dr. Maher, how many people in the world have Birt-Hogg-Dube syndrome and when was it first described?

DR. EAMONN MAHER:

That is a very tough questions because we know; for example, we just had a study between ourselves in Netherlands and each had about 50 odd families, but the population of the UK is much higher than that of the Netherlands, so we think that we are grossly under ascertaining families in the UK. It was already described in the late 1970s and it's only really becoming more prominent, I think, over the

last 5 or 6 years as the genetics diagnosis has enabled more families to be recognized.

DR. BRUCE BLOOM:

And some scientists like you, I think, believe that it is very much under-diagnosed, why is that, what is it we just found out and how is it helping us to classify patients as having this syndrome?

DR. EAMONN MAHER:

One of the reasons we think it is undiagnosed is because it became very difficult to recognize, so we see people in clinic who; for example, presented with kidney tumor andnobody suspected that they had Birt-Hogg-Dube syndrome and if anyone is looking very carefully, you can pick up other features in the serial order as history of pneumothorax or the skin lesions. What has enabled to diagnosis to be more accurate is the molecular genetic testing that has been available for a few years since the identification of the gene and that allows us in patients who have a doubt about the diagnosis to do mutational analysis and in many cases, identify the underlying mutation.

DR. BRUCE BLOOM:

Mr. Solly, why have you chosen and when I say you, I mean the entire Myrovlytis Trust, to focus on this particular orphan disease?

DR. JOHN SOLLY:

Very few reasons, the first exact reason I placed it is that the fields of funding for the trust has a particular interest in BHD syndrome and then the second reason is that at the Myrovlytis Trust, we are motivated by the idea or the quality of opportunity. To us it's unclear why it should be that if you have a genetic mutation that happens to be rare, why the drugs available and why the quality of treatment should be inferior from somebody who has a much more common genetic disorder. We feel that always it should be the same for everybody.

DR. BRUCE BLOOM:

Dr. Maher, could you describe for us the major symptoms and organ symptoms that are affected in BHD and when these symptoms generally first appear in the patients?

DR. EAMONN MAHER:

Probably, the commonest feature is the appearance of small whitish papules over the face and sometimes over the upper trunk. These typically arise with time in the early 20s, often to say that, it may not be noticed by the individual concerned and in some cases, they can be very prominent and they can cause difficulties with their cosmetic appearance in some cases, but after often they are like unobtrusive and may not be commented on particularly by family members, etc. The other common features is pneumothorax, so patients will present with pneumothorax and often have recurrent pneumothorax from bullae in the lung; now again typically in the 20s is when we first see these, the average age for both of those features is in the 40s, but I think its difficult to say, precise the amount of skin lesions developed because they are often overlooked for a long time and then perhaps the most serious complication is risk of kidney tumor including renal cell carcinoma and average age for developing that is again in the 40s, but it can occur in the 20s or it may occur for the

first time in the 60s. Overall, only minority may be 20% to 30% of all patients will develop kidney tumors.

DR. BRUCE BLOOM:

So let's look more closely what's going on with the skin? What specifically are these lesions and why do we think they appear?

DR. EAMONN MAHER:

Well, the most common pathological diagnosis is a fibrofolliculoma, so there are benign tumors of the hair follicle and as to why they should appear, we know that the Birt-Hogg-Dube gene is a tumor suppressor gene, but why particularly inactivation of this gene should cause these particular tumors is unclear at the moment.

DR. BRUCE BLOOM:

You think there's a possibility that there are other genetic defects potentially in these 3 organ systems along the hair and skin follicles and the kidney that might be associated with the other genetic defect we already know about?

DR. EAMONN MAHER:

I think the primary cause is the mutation in the Birt-Hogg-Dube gene, the folliculin gene, but obviously if we have a kidney tumor, then we know that by the time we have a full blown tumor there will be multiple genetic lesions in a tumor and so the initiating factor will be loss of function of the folliculin tumor suppressing gene, but subsequently there will be other mutations occurring really haven't been studied very well for the fibrofolliculomas as to what additional events will be going on there, but these additional events occur and perhaps other genetic factors may modify how severely a person is affected whether they develop kidney tumors or not, but basic underlying cause is the mutation of the folliculin.

DR. BRUCE BLOOM:

And are there any treatments that are advised for these skin lesions through surgery or is there any other treatment that can be done?

DR. EAMONN MAHER:

Mainly, just say, cosmetic reasons. Various treatments have been used, but typically the one that would be used would be laser or sometimes just shaving them off. Often as I say, they are not that cosmetically obtrusive and people don't seek treatment for them.

DR. BRUCE BLOOM:

And Mr. Solly, is the Myrovlytis Trust interested in finding treatments, preventions, better diagnostics for this disease and diseases like it?

DR. JOHN SOLLY:

Say, put BHD as a whole says as a diagnosis as Eamonn mentioned, we think the primary cause is mutation in the BHD gene and/or in the folliculin gene and so we think that's pretty much mapped out. The diagnosis we think is pretty much that. We are very interested in finding treatments for sure. I don't know that you could call them cures that sounds as a step too far, but we will be very interested in finding drugs or some other therapy as a means that inheriting the mutation in the BHD gene doesn't adversely affect your life. Eamonn says that a lot of this skin lesions aren't particularly cosmetically disfiguring, you know, that's often very true, but there are occasions if that degree is available in different people where they can't cause a certain amount of emotional distress, so if we can alleviate that, that's obviously a good thing if we can remove the risk of pneumothorax, again not obviously a good thing and if we can remove this 20 to 30% risk of kidney tumors including renal cell carcinoma or we can push it out so that the chances are, you know, that something else will get you, then that has to be a good thing.

DR. BRUCE BLOOM:

Dr. Maher, what do you think causes the lung cysts and what do we do about those?

DR. EAMONN MAHER:

Again, this is another one of those parts of Birt-Hogg-Dube syndrome that there is relatively little information on. I suspect it's got something to do with that developmental abnormalities as a result of abnormal signaling in the lung, but there is very little research being done on it.

DR. BRUCE BLOOM:

What kind of issues does it cause in patients?

DR. EAMONN MAHER:

If the cause is recognized as being pneumothorax and as you know that the treatment can be relatively straight forward and so it's important that all Birt-Hogg-Dube patients all who have the possibility of pneumothorax, so if they get short of breath, they can seek medical attention. In some patients, they will go on to get recurrent pneumothoraces and not that will require pleurodesis to fix their lung in and prevent them getting set the pneumothoraces.

DR. BRUCE BLOOM:

And what percentage of patients actually have the skin lesions and the lung cysts, is it high percentage or small percentage?

DR. EAMONN MAHER:

Yeah, eventually a high percentage will have it, so the majority of patients will have it. I think with the skin lesions again it becomes quite difficult because if you don't see the patients and don't look very carefully for them, they may not be available. Having said that

there are certainly some patients who may, for example, just present with an acute tumor, who don't appear to have any evidence of the skin lesions.

DR. BRUCE BLOOM:

So let's turn our attention to those kidney tumors and the other things that are going on in the kidneys. What specifically do we see in BHD patients? What kind of kidney tumors do they get and are those tumors similar to in general the kinds of kidney tumors that patients get?

DR. EAMONN MAHER:

That's an interesting question and initially when the tumors were first recognized, they were described as oncocytomas and then the pathology was very carefully reviewed and they were shown to have to be atypical for more distinctive features. Actually what we tend to do is to put the emphasis more on the fact that recent work shows that the histopathology can be much more variable and can actually include clear cell tumors, so clear cell kidney cancer is the most common form of kidney cancer in the population and for well only a minority of patients with Birt-Hogg-Dube syndrome will develop the clear cell form of kidney cancer. We attempted to put on the emphasis that because of the variability, there is isn't one particular form of kidney cancer that you could say, couldn't be Birt-Hogg-Dube, so really in patients with a family history of kidney cancer at a very young age or bilateral tumors, we then emphasize that Birt-Hogg-Dube should be considered as the possible course even if the histopathology isn't typical.

DR. BRUCE BLOOM:

So would we do a screening test for every patient that had that kind of kidney cancer to see if they had Birt-Hogg-Dube genetic defect, will that be sensible?

DR. EAMONN MAHER:

I think there is a case for that. When we recently did a study where we took a series of patients who we had seen over many years, we collected DNA samples from them because we felt they had an underlying genetic cause for kidney cancer selective by either they had a family history or they had bilateral tumors or they had kidney cancer at a young age. So we suspect that there was an underlying cause that we couldn't identify one of the well-known causes. So we went back to the samples and we did mutation analysis of the folliculin gene and we found just in the 5% of these actually had a mutation in the Birt-Hogg-Dube gene.

DR. BRUCE BLOOM:

So does everyone who has this defect in folliculin get classified as a patient that has BHD syndrome?

DR. EAMONN MAHER:

I think for the moment we would say there will be found folliculin gene mutation in an individual that we would consider them at risk of developing all features of Birt-Hogg-Dube syndrome. It may be in time, we recognize that that mutations are only associated with specific features of the disorder, but I think it would be a bit premature to speculate or not of the moment in Birt-Hogg-Dube, so for

example, some patients have been described as presenting just with familial pneumothorax and when the mutation analysis had been done and the mutation in Birt-Hogg-Dube gene has been identified, in many cases, it hasn't been obviously different from mutations that have been seen in patients who presented with straight forward Birt-Hogg-Dube syndrome. So it's too early to say that specific mutations might cause a specific phenotype.

DR. BRUCE BLOOM:

I would like to thank our guests, Mr. John Solly, charity manager of the UK's Myrovlytis Trust and Dr. Eamonn Maher, profession of medical genetics at the University of Birmingham in UK for joining us to discuss the diagnosis and treatment of the orphan disease, Birt-Hogg-Dube syndrome.

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