ADPKD Education Case Rounds

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Case example #1:

- 46-year-old Woman.
- On Tolvaptan: 30mg in the morning and 15mg in the afternoon. Not a full dose and just barely tolerating
- Drinking 6-8L of fluid per day with urine osm 78.
- On 45mg, can't tolerate even 15mg more 8 hours later.

What is most important?

1. Repeat doses to ensure drug effect all day? So change to 30/15?
2. Just focus on what dose keeps osm <100. So maybe even reduce to 30mg daily to improve quality of life if osm<100 on that dose?

Discussion:

- When we talk about large volumes of urine, there are a group of people in the 8-9L/day range.
- 1st item to consider – what the patient can manage.
- 2nd item – Tempo study/publication – urine osmolarity threshold (DOI:10.1681/ASN.2016040448)
- KDIGO guideline– as a 'purist' titrate to the maximum tolerated dose as was done in the clinical trials.
    - It is unclear that the aquaretic dose is the same as the cyst inhibition dose, and likely is very different (recall, doses are much lower when used for hyponatremic CHF) – so aim to titrate up for cyst inhibition.
    - From the same study, one inisight is that the people with the greatest aquaretic symptoms also get the greatest renal benefit. In part due to starting early in the disease when concentrating capacity is intact. So people with the largest difference between pre-treatment Uosm and post-treatment get both the greatest treatment effect and most symptoms
    - Most are not using urine osmolarity to titrate dosing anymore.

- Goals – titrate to the highest tolerated dose.
    - One tip is that if the patient already has a maximally dilute urine (ie Uosm close to or below 100) you can likely titrate as much as you want and the patient likely won't notice the difference since they are already maximally dilute
- Largely go by symptom tolerance. A bit easier to up titrate when you start at lower doses and slowly take them up. Options for dosing: 45mg and 15 mg, 15 mg and 15 mg, 30mg and 15mg
- Allow drug holidays to make it part of their life. Will be on the drug forever to see a benefit. If the drug is ruining their life or ruining major events, more likely to lose the patient from therapy. Have patients on 15mg and 15mg and urinating 12L/day. Could likely titrate up, but

that same patient at 45mg and 15mg couldn't tolerate. Wouldn't hesitate to go even lower with split dosing if they can't tolerate

- Most agreed we would not do once a day dosing – there are concerns of 'rebound' in that the drug will trigger a compensatory increase in vasopressin which is then not antagonized much of the time and may theoretically actually hasten disease progression compared to not taking it at all. Go with highest possible maximum tolerated dose but avoid once a day dosing.
- Establish expectation of increase dose at the get-go with patient
- Other strategies to manage aquaretic symptom burden:
    - Nocturia – dietitians are key. Decrease salt and protein. Most successful – protein heavy meal at lunch not dinner so that osmolal load later in the day is lower.
    - Drug timing very important. Close gap between the two doses (a little shorter than 8 hours) to stack earlier in the day.
    - What's the person's job and can they get to a washroom?

Case example #2:

- 42 year old Women, ultrasound for pregnancy, no family history.
- Multiple simple cysts/liver cysts incidental (sub-centimetre), kidneys not enlarged.

Should genetic testing be ordered?

Discussion:

- How many cysts? More than 10. Likely PKD but not enough to confirm in the setting of no family history so genetic testing can be helpful
- Be aware of the possibility of a non-diagnostic test. There are frequent variants of uncertain significance (VUS's) and even ~ 10% of established ADPKD cases based on clinical criteria will not have a clear genetic diagnosis and still be unresolved. So genetic testing may be helpful, but the possibility remains that you may still not have a clear diagnosis

Testing logistics:

- In the application you must indicate that genetic testing will change short-term management.
- Remote/rural labs won't be able to do processing similar to IGRA's where 1 lab in HA does that.
- Action item: ADPKD team to follow-up with genetics regarding logistics of getting testing done e.g. blueprint, lab requirements, access. Does genetics have a lab list where testing can get done?