Twitter Thread by Robert Centor

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@medrants

1/ The classic presentation at morning report for hypercalcemia starts with polyuria, constipation and confusion. #UncleBob wanted to understand why - stimulated by @CuriousClinPod ? @HannahRAbrams @tony_breu @AvrahamCooperMD

2/ Let's start with confusion. Finding information on this is very non-specific but I think this quote helps: High calcium levels can be a catalyst for neuronal demise, possibly due to glutaminergic excitotoxicity and dopaminergic and serotonergic dysfunction.

3/ But colleagues and learners know that I am most interested in the polyuria. I have taught that hypercalcemia can cause nephrogenic diabetes insipidus, but the mechanism was unclear. Let's review how ADH works and then look at an interesting study that suggests an answer.

4/ Antidiuretic hormone stimulates water reabsorption: stimulating insertion of "water channels" or aquaporins into kidney tubule membranes which transport solute-free H20 through tubular cells & back into blood, -> decrease in plasma osms and an increase urine osms.

5/ Thus we need to stimulate ADH production and have aquaporins (specifically aquaporin-2) available for transport. In general nephrogenic DI occurs because of the lack of aquaporin-2(AQP2).

6/ How does this happen with hypercalcemia? I found this article: Hypercalcemia induces targeted autophagic degradation of aquaporin-2 at the onset of nephrogenic diabetes insipidus - Kidney International https://t.co/0l87zvTnZj

7/ So now we have to understand autophagy! From the article: Autophagy is a highly conserved biological process that involves removal of protein aggregates and damaged organelles and the subsequent transport of these components to the lysosome for degradation

8/ Hypercalcemia causes protein degradation. This occurs for many proteins, and specifically AQP2. Degradation occurs very rapidly in animal models. Thus, patients will have dilute urine because ADH cannot interact with the missing AQP2.

9/ As an aside, this likely also occurs with hypokalemia (but not as dramatically). The animal studies also show that once the hypercalcemia resolves, AQP2 quickly returns to normal levels.

10/ The constipation likely occurs secondary to the volume contraction from the polyuria. This can be severe enough to elevate to obstipation.

11/ Lowering the calcium level to normal resolves these symptoms. I hope this discussion of mechanisms makes sense.