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Nephrogenic diabetes insipidus: update of genetic and clinical aspects

Sei Sasaki

Department of Nephrology, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

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Introduction

Ten years have passed since the cloning and molecular identification of the vasopressin V2 receptor (V2R) and aquaporin-2 water channel (AQP2), a pair of molecules whose genetic mutations have been established to cause hereditary nephrogenic diabetes insipidus (NDI), a human disease characterized by an inability to concentrate urine. Gene identification and mutation searches in NDI families have led to the identification of numerous patients, which in turn has provided a more detailed view of the clinical characteristics of this disease entity. Human genetic analyses of these types have also provided insight into how AQP2 protein is regulated inside the cell and how mutant AQP2s come to resist proper regulation. This knowledge of cellular biology will form the basis for the development of new treatments. The present Comment focuses on recent advances in our understanding of the genetic and clinical aspects of NDI.

Classification

NDI patients typically cannot concentrate urine above serum osmolality, and thus manifest polyuria and polydipsia. NDI can be classified into two major categories: hereditary (or congenital) and acquired (Table 1). Hereditary NDI is a rare disorder that is generally diagnosed soon after birth or in childhood, by paediatricians. As a result, most ‘adult’ physicians seldom see this disorder. Loss-of-function mutations of the V2R gene are responsible for most hereditary NDI (~90% in the Quebec area of Canada).

Table 1. Classification of NDI

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Defective gene</th>
<th>OMIM</th>
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</thead>
<tbody>
<tr>
<td>X-linked</td>
<td>V2R</td>
<td>304800</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>AQP2</td>
<td>222000</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>AQP2</td>
<td>125800</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
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<tr>
<td>Lithium, demeclocycline, amphotericin, methoxyflurane</td>
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<tr>
<td>Hypocalcaemia</td>
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<td>Hypokalaemia</td>
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<tr>
<td>Ureteral obstruction</td>
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<tr>
<td>Miscellaneous</td>
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</tbody>
</table>
The incidence of V2R NDI is 8.8 per 1 million male births in that region [1]. The V2R gene is located on the X-chromosome and patients exhibit X-linked inheritance. While only males are symptomatic among patients with X-linked inheritance, females with heterozygous mutations (carriers) sometimes present with mild NDI symptoms due to variable inactivation of the mutated gene (Lyon mechanism). More than 170 different mutations are known for V2R NDI, and the mutations spread throughout all portions of the protein [1]. Information on the mutations is available in online databases such as OMIM (www.ncbi.nlm.nih.gov/Omim/) and HGMD (www.hgmd.org/).

Most of the remaining forms of hereditary NDI are caused by mutations of the AQP2 gene located on chromosome 12, and both recessive and dominant inheritance patterns have been reported [2]. To date, 22 different mutations have been found for the recessive type and five mutations for the dominant type. Dominant inheritance seems to be related to its genotype; the causative mutations are all located in the C-terminal of the AQP2 protein [3,4].

Several other genes yet to be proven might also be responsible for hereditary NDI. Recently, we analysed 34 families with hereditary NDI and found V2R mutations in 22 families and AQP2 mutations in six families. No mutations were found in V2R or AQP2 in the other six families. Urine-concentrating ability depends on two factors: interstitial hypertonicity in the renal medulla and water permeability of the collecting duct. Both factors are products of a number of events. For example, the water permeability of the collecting duct is controlled by the binding of circulating vasopressin to V2R at the basolateral membrane, an event that activates cAMP-dependent and other signalling pathways, resulting in accumulation of AQP2 at the apical membrane. Thus, mutations of any of the proteins that form this cascade might also be responsible for NDI. Targeting certain genes in mice has also been shown to cause NDI. Knockout of AQP1, 3 and 4 resulted in defects in urine concentrating ability by varying degrees [5]. The molecules responsible for the generation of medullary hypertonicity such as CLC-KA (a chloride channel of the thin ascending limb of Henle) and aldose reductase similarly showed an NDI phenotype when the genes were targeted [6,7]. However, no mutation of these genes has been found in human NDI patients, with the exception of a very mild phenotype in AQP1 null subjects [8].

Acquired NDI can be induced by several drugs (Table 1). Lithium is the most frequently used drug among those capable of inducing acquired NDI and, thus, is important in clinical practice. The incidence seems to increase as the therapeutic period grows longer. Hypercalcaemia and hypokalaemia are also known to cause defects in urine concentration. Studies in experimental models have shown a decrease in AQP2 expression at the apical membrane of the collecting duct in these disease conditions [9].

### Clinical symptoms and diagnosis

The defect of NDI is an inability of the kidney to concentrate urine in response to endogenous and exogenous vasopressin. The main symptoms include polyuria, polydipsia, dehydration, vomiting and hypotonia. Symptoms of hereditary NDI usually appear soon after birth, and patients sometimes manifest fever as well as physical and mental retardation due to dehydration. Hydronephrosis and resultant renal dysfunction are occasionally observed later on in childhood [10]. Nocturnal enuresis is one of the symptoms of hereditary NDI [10], but V2R and AQP2 are both unrelated to another hereditary disease called primary nocturnal enuresis (OMIM 600631) [11].

Hereditary NDI seems to have the uniform clinical manifestations described above, but this might only reflect the information on screened patients with clear clinical presentations. It may be that a milder form of NDI has been overlooked due to a lack of genetic identification. A recent study demonstrated that some V2R mutations showed milder symptoms even within the same families. In one family, for example, the severity of urine concentrating defects varied among affected brothers [12]. We also observed a boy affected by the dominant AQP2 mutation, who could concentrate urine above 400 mOsm/kg water [3]. Thus, it may be possible that the further identification of new patients with genetic disease confirmation will provide a wider clinical picture of NDI. In this context, gene mutation analysis should be considered even in patients with mild NDI symptoms. Fortunately, both V2R and AQP2 genes are small and can be easily analysed.

Acquired NDI may be overlooked and does not present significant problems as long as the patients can drink water freely. Physicians should take care not to overlook NDI in older subjects who take lithium medication and subjects with conditions that inhibit free access to water such as unconsciousness or surgery [13]. It should be noted that urine concentrating ability is not easily recovered after lithium withdrawal. In some cases, the defect has been found to persist for more than 5 years [14].

### Therapy—usual therapy and future challenge

For hereditary NDI patients, early diagnosis (preferably genetic diagnosis) and adequate therapy are important to prevent physical and mental retardation. The goal of NDI therapy is to reduce urine volume. This is achieved by reducing salt intake and administering thiazide diuretics in combination with amiloride and/or indomethacin [10]. Thiazide inhibits salt reabsorption in distal convoluted tubules, which causes mild hypovolaemia without affecting the hypertonicity of renal medulla. Hypovolaemia stimulates fluid reabsorption in the proximal tubules, resulting in less fluid delivery to the distal tubules and
collecting ducts where urine is concentrated. Amiloride works similarly, and indomethacin decreases prostaglandin synthesis, thereby attenuating the vasopressin-inhibiting effect of prostaglandin. Indomethacin is sometimes not an option due to side effects such as gastrointestinal bleeding, but side effects of this type can be avoided by the use of COX-2 inhibitors [15]. These traditional therapies established for hereditary NDI are equally applicable to acquired NDI. Amiloride may be more preferable in lithium-induced NDI as this drug inhibits lithium entry into the cell by blocking the epithelial Na channel.

Once the NDI-causing mutations were identified, researchers began to perform extensive cell biological studies to ascertain how they could cause loss-of-function. Although such studies are generally prompted by scientific interest, the results obtained may establish a direct link to the therapy of NDI treatment if substances or strategies that correct defective V2R or AQP2 functions are discovered. Most V2R mutant proteins are synthesized, but retained in the endoplasmic reticulum (ER) and do not reach the cell surface [16]. Other types of defects, for example inhibition of protein synthesis, reduced affinity to vasopressin, and inability to transduce cell signalling, are relatively rare. Mutant proteins are conformationally different from the wild-type protein, and this difference is detected by the ‘quality controller’ of the ER. This event is known not to be unique for V2R, as other hereditary diseases such as CFTR and α1-antitripsin deficiency have been shown to share the same molecular pathological mechanism [17]. A recent study demonstrated that the cell-permeable V2R antagonist, SR121463A, could rescue the mutant V2R proteins retained in the ER [18]. This drug may bind to misfolded proteins and correct the conformation in the manner of a chaperone, thereby allowing further transport beyond the ER. The mutant V2R proteins were shown to be functional at the cellular level, thereby offering compelling evidence that this or similar drugs will be potentially useful for clinical application. In this respect, knowing the exact kind of mutation by genetic analysis has immediate clinical relevance for NDI patients.

Similarly, most autosomal recessive AQP2 mutations responsible for NDI were found to be retained in the ER [2]. Further searches for chaperone-like substances, for example, like SR121463A in the case of V2R-defect NDI, are necessary and are currently underway. In the case of autosomal dominant NDI, our recent study in three families showed that mutant AQP2 proteins are mistransported to the basolateral membrane instead of the apical membrane [19]. Given that the identified mutations are all located in the C-terminal portion of the protein, the mistransport indicates the importance of the AQP2 C-terminus in determining the routing. Intracellular AQP2 transport is very likely mediated by interactions of the C-terminus with other undefined proteins. Studies on the mechanisms of this deranged transport should also open ways to treat this type of NDI.

Conflict of interest statement. None declared.

References