VI Seminario Nazionale per Dottorandi in Farmacologia e Scienze Affini
Siena, Certosa di Pontignano, 23-26 Settembre 2002

IDENTIFICATION OF A NOVEL MISSENSE SUBSTITUTION IN THE VASOPRESSIN-NEUROPHYSIN II GENE IN AN ITALIAN KINDRED WITH FAMILIAL NEUROHYPOPHYSEAL DIABETES INSIPIDUS

Cennamo L., 1° anno del Dottorato di Ricerca in "Scienze Farmacologiche e Fisiopatologia Respiratoria", XVII Ciclo. Durata del Dottorato in anni: 4. Sede di servizio: Dipartimento di Pediatria, II Università di Napoli.

INTRODUCTION

Autosomal dominant neurohypophyseal diabetes insipidus (ADNDI) is a rare hereditary disease characterised by excessive thirst and by excretion of abnormally large volumes of dilute urine. The disease is due to a mutation in the arginine vasopressin-neurophysin II (AVP-NPII) gene, resulting in a defective preprohormone and a deficiency of AVP. ADNDI reduces not only the plasma levels of AVP, but also the amount of AVP stored in the posterior pituitary, as evidenced by the absence of the characteristic high signal intensity of the posterior pituitary in T1-weighted magnetic resonance images of most ADNDI patients.

The arginine vasopressin-neurophysin II (AVP-NPII) gene consists of three exons. The first exon encodes putative signal peptide, AVP and NH2-terminal region of neurophysin II (NPII); the second exon accounts for the central region of NPII and the third exon gives rise to the COOH-terminal region of NPII and glycoprotein. AVP is synthesized by magnocellular neurons of the supraoptic and paraventricular regions of the hypothalamus as pre-pro hormone. Pro-VP is generated by the removal of the signal peptide from preproVP during cotranslational translocation and is released into the lumen of the endoplasmic reticulum. It is subsequently transported within neurosecretory vesicles to the axon terminals in the neurohypophysis via the regulated secretory pathway yielding AVP, NPII and glycoprotein. They are released into the circulation in response to serum hypersmolality, hypotension or hypovolemia.

METHODS

The affected subjects noticed the onset of polyuria and polydipsia when they were between 4 and 6 years of age. None of the children experienced an acute episode of dehydration or failure to thrive. Before the genetic testing, the diagnosis of ADNDI in a subject (IV2) was missed because the 8-h water deprivation test performed at 4 years of age were normal. Contiguous thin slice (3-mm thickness) T1-weighted sagittal and coronal images of the posterior pituitary, with and without fat saturation, were performed during MRI scanning

After written informed consent was obtained from the subjects, genomic DNA was extracted from peripheral blood leukocytes following standard procedures. Each of the three exons of the AVP-NPII gene was amplified by PCR using the primers previously described. DNA sequencing of PCR products was performed using the sense primer, an ABI 310 DNA Sequencer and the ABI PRISM Dye Terminator Cycle Sequencing Reaction Kit (Perkin Elmer, Milan, Italy) according to the manufacturer's instruction.

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