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Focal segmental glomerulosclerosis in solitary kidney in WAGR syndrome

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Abstract: WAGR syndrome consists of Wilms' tumour, aniridia, genitourinary malformations and mental retardation, and is associated with chromosomal microdeletion of 11p13. We report a case of young male, exhibiting several typical features of WAGR syndrome (e.g. WT, aniridia and genitourinary abnormalities), but missing some other (mental retardation and chromosomal abnormality absent). Renal biopsy performed in our patient for unexplained proteinuria showed focal segmental glomerulosclerosis, presumably of secondary origin; the decrease of proteinuria was achieved by the firm control of BP in conjunction with the reduction of body weight.

Key words: Focal segmental glomerulosclerosis – Gene – Tumour – WAGR syndrome

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Introduction

In March 2001, a young man (born in 1980) was admitted to First Department of Medicine, with a suspicion of WAGR syndrome, suffering from proteinuria and mild renal insufficiency.

Family history was indifferent: father (born in 1945) underwent myocardial infarction and was treated for gastric ulcer; mother (born in 1953) was treated for coronary disease and chronic arthralgias. No case of inborn developmental defect and/or renal disease was identified in the family.

Some data from the past history suggested the presence of a major developmental defect. Born in 1980 after the first physiological gravidity and delivery (weight 3400 g and height 49 cm) the patient did not suffer from any apparent medical problem, apart from the neonatal jaundice, till the age of two months. At that time the first symptoms of a developmental defect were eye complications. In the early postpartum period the signs of nystagmus were noticed, aniridia and glaucoma were diagnosed thereafter. In 1987 only minor light perception on left eye remained. In 1992 he underwent surgery of the right eye for cataracta and thereafter numerous cyclocryocoagulations. The loss of visus was completed in 1993 and in 1996 he underwent bilateral bulbar enucleation for glaucoma dolorosa. In 1986 he was successfully resuscitated for cardiac arrest that he suffered during tonsillectomy. The discovery of tumour in the kidney was another early finding: Wilms' tumour (WT) on the right side was disclosed in 21 month of the child's age. Soon after (7/1982) a surgery of WT followed (nephrectomy, diagnosis of WT confirmed histologically) in conjunction with chemotherapy and radiotherapy (which was stopped in 9/1984) with long-term oncological follow-up.

Since 1990 small amount of protein was detected in the urine. After the increase of the proteinuria to the level of 4 g/24 hours in 1994, serie of five pulses of cyclophosphamide was given in the paediatric department, however without any clear effect on the level of proteinuria. Other clinical complications include abnormalities of bone calcium and phosphate metabolism (scoliosis, rib luxation, osteoporosis, asymmetry of the length of lower limbs) and genitourinary anomalies (cryptorchidism – the right testis was not found during surgical evaluation, hypergonadotropic hypogonadism, gynecomasty – treatment with tamoxifene unsuccessful). The final appearance of genitourinary tract was markedly affected by surgical procedures (left side semicastration in 1996 and plastic surgery of breast in 1998). In 2001 a surgery of osteochondroma from right hip was performed. From the digestive disturbances the dyspeptic syndrome of higher type predominated, hiatus hernia, frequent episodes of ileus or subileus, in 1999 he underwent cholecystectomy for cholecystolithiasis. From 1994 he was treated for arterial hypertension and dyslipidaemia, which were corrected by the antihypertensive, resp. hypolipidemic drug therapy. From

the social point of view – he graduated from economic high school for blind people. No major complaints were registered on admission.

Present problems – the novel onset of nephrotic syndrome in context of renal insufficiency (serum creatinine 350 mmol/l) – lead to the decision to perform renal biopsy (RB). Physical examination revealed: obese young male (height 170 cm, weight 88 kg, body mass index 31.2), with clinical features of Cushing's syndrome and with moderately elevated blood pressure (140/80 mm Hg). Of note were multiple scars – sequelae from surgical interventions, missing (enucleated) bulbi, genitourinary anomalies (missing testes and scrotum, gynecomasty), asymmetry of the legs (left leg shorter for 2 cm than right leg), perimaleolar oedema. The biochemical analysis showed serum creatinine 104–152 mmol/l (a decrease in comparison with the previous analysis), hypoproteinemia (56 g/l) and hypalbuminemia (33 g/l), higher triglyceride (5 mmol/l) and cholesterol (7.2 mmol/l) plasma levels in conjunction with urinary protein excretion of 6.8 g/24hours, creatinine clearance of 1.04 ml/s (corrected).

Other biochemical parameters (including immunology) were normal. Renal ultrasound revealed solitary left kidney, with normal size (12 cm in the long axis) and parenchymal width, and few small cysts. Renal biopsy (RB) showed 4–5 enlarged glomeruli, some of them with thickening of Bowman's capsule, and all of them presenting irregular enlargement of axial matrix with borderline hypercellularity. In several glomeruli apparently activated podocytes and in two glomeruli tinny sclerotization of vascular pole, with adhesions to capsula, were observed. Most capillaries were enlarged and their glomerular basement membrane moderately thickened. Electron micrograph disclosed smooth thickened glomerular basement membrane, frequent fusion of foot processes and enlargement of mesangial axial matrix. No changes typical for diffuse mesangial sclerosis were found. Conclusion from RB: initial stage of focal segmental glomerulosclerosis (FSGS), probably modified by arterial hypertension.

Based on histology from RB and on the clinical finding of solitary kidney in obese patient (aside from the impact of arterial hypertension) the likelihood that FSGS was secondary was high and the indication of immunosuppressive treatment was not substantiated. Rigorous control of BP, achieved with angiotensin receptor antagonist therapy in conjunction with the reduction of body weight, resulted in a decrease of proteinuria (below 3 g/24 h) and stabilization of renal function (serum creatinine lower than 200 mmol/l). From April 2001 by the end of the year 2002 the patient suffered from pericarditis and more recently from abnormal movements of higher extremities, highly suggestive of psychogenic origin. He was also examined for endocrinous problems (hyperprolactinemia and iatrogenic Cushing's syndrome).

In October 2002 he committed unsuccessful suicidal attempt, provoked, at least partly, by the fact, that his parents had divorced.

Genetic investigation

Genealogy: parents healthy, non-relative (father 35 years old and mother 27 years old at the time of birth of the proband); in the genealogy 1× gastric cancer, 1× carcinoma of lung, 1× carcinoma of gastrointestinal tract, 1× carcinoma – non specified, 1× non-insulin dependent diabetes mellitus.

Dermatoglyfs of the proband and of the proband's mother slightly abnormal (Sydney line, higher TRG in mother), father not examined.

Cytogenetics: chromosomal investigation repeatedly normal, caryotype 46, XY, deletion 11p(13) not found (GTG banding, HRT analysis with detection sensitivity 750).

Intelligence quotient (IQ) in the lower range.

Developmental milestones: he started walking in 12 months, developmental milestones normal by the age of 22 months, when admitted to hospital for WT, treated thereafter for two years. He started to attend the school from the age of 8 years; in the 1st class he changed the normal school for the school for blind people. He had to repeat the first and third year of attendance due to frequent absences at school.

Discussion

The patient presented herein, exhibits some typical features of WAGR syndrome, albeit differs in some aspects from the patients (pts) reported previously. WAGR syndrome is an acronym for a congenital developmental defect consisting of Wilms' tumour, aniridia, genitourinary malformations and mental retardation. So far no more than few hundreds of pts were described throughout the world. (Micro)deletions of the short arm of chromosome 11 at band 11p13 are typical chromosomal aberration found in virtually all affected patients. The Wilms' tumour gene (WT1) encodes a zinc-finger transcription factor involved in the development of the kidneys and gonads and their subsequent normal function. Mutations in the WT1 gene were consistently identified in patients with WAGR syndrome, Denys–Drash syndrome (diffuse mesangial sclerosis, pseudohermaphroditism, WT) and Frasier syndrome (glomerulopathy with gonadal dysgenesis in female with 46, XY genotype) [1].

The trias of aniridia, WT and genitourinary abnormalities revealed early after the birth in our proband, and this association strongly suggested the diagnosis of WAGR syndrome. Our patient did not exhibit mental retardation, which is also listed as a feature of WAGR syndrome. In fact his intellectual abilities were considered as "normal", even if lying in the lower range of the normal IQ. This arises the question of an appropriate testing of mental and intellectual capacity in a patient with visual impairment, which is otherwise seriously debilitated too. Thus, it cannot be excluded, that retardation is not in fact an integral part of this syndrome. On the opposite, the obesity was observed not only in our patient, but in many other similar patients and was suggested

unequivocally by some [2] even if with high degree of reticence by others [3] to be possibly a feature of the syndrome. What makes the problem more complicated is the fact, that our patient, and possibly other pts too, has been treated with corticosteroid therapy and exhibits clinical features of the Cushing's syndrome.

Even though our patient was tested twice for chromosomal anomaly of 11p13 microdeletion type, the results of cytogenetic evaluation were repeatedly negative. Fluorescent "in situ" hybridization (FISH) or other more sensitive chromosomal analysis might be helpful to confirm definitely the absence of such a paramount anomaly [4].

Relatively unique is our finding of histological changes observed in the renal biopsy specimen. While some data on the incidence of renal failure in WAGR syndrome and/or in WT have been published [5], information concerning histological changes in the kidney contralateral to the kidney being removed for WT is currently missing. The histological finding of FSGS (presumably of secondary origin) could "fit" to explain the proteinuria in our patient when taken into consideration the whole clinical setting (note the response to the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist administered after the renal biopsy was performed), and moreover could be probably expected at least in some of other pts with WAGR syndrome.

Suicidal attempt in our patient should serve as a memento for all who could feel to be involved, to find an effective treatment for such a frustrating condition.

In conclusion: we presented a young male, exhibiting several typical features of WAGR syndrome (e.g. WT, aniridia and genitourinary abnormalities), but missing some other (mental retardation and chromosomal abnormality – microdeletion of 11p13 absent). RB performed in our patient for unexplained proteinuria showed FSGS and yielded some new information concerning morphologic changes occurring in patients with WAGR.

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