Clinical Medicine Insights: Case Reports

CASE REPORT

Abnormal Cystatin C Levels in Two Patients with Bardet-Biedl Syndrome

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Abstract: Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder characterized by central obesity, mental impairment, rod-cone dystrophy, polydactyly, hypogonadism in males, and renal abnormalities. The causative genes have been identified as BBS1-14. In the Western countries, the prevalence of this disease ranges from 1/13,500 to 1/160,000, while only a few Japanese patients have been reported in the English-language literature. The incidence of renal dysfunction or anomalies in previous reports varies considerably ranging from ~20% to universal occurrence. We here report that two Japanese patients who had BBS with normal BUN and creatinine levels had elevated levels of cystatin C, a sensitive marker of glomerular filtration rate. A urine albumin level increased only in the elder patient. Thus, cystatin C may be useful for detecting renal abnormalities in patients with an apparent normal renal function. Because this disease is diagnosed by accumulation of symptoms, such a sensitive marker might help early diagnosis of BBS.

Keywords: mental impairment, obesity, cystatin C, renal abnormality, retinitis pigmentosum

Clinical Medicine Insights: Case Reports 2011:4 17–20

doi: 10.4137/CCRep.S6622

This article is available from http://www.la-press.com.

Introduction

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder characterized by central obesity, mental impairment, rod-cone dystrophy, polydactyly, hypogonadism in males, and renal abnormalities.[1,2] The causative genes have been identified as BBS1-14 genes that encode proteins possibly linked to cilia function, but more than 20% of patients have no mutations found.[3] The diagnosis is made only by the clinical phenotype with the presence of at least three major symptoms, however, it is often difficult partly because of age-dependent development of some symptoms. In the Western countries, the prevalence of this disease ranges from 1/13,500 to 1/160,000.[3] By contrast, only a few Japanese patients have been reported in the English-language literature.[4–6]

Renal fibrosis is one of the most devastating symptoms, ultimately leading to chronic renal failure requiring hemodialysis.[7] The incidence of renal dysfunction or anomalies in previous reports varies considerably ranging from ~20% to universal occurrence.[2,7] An early detection of such abnormalities may be important for patients and guardians to prepare them. It may also be useful for prompt correct diagnosis of BBS, since the diagnosis of this disease is based on the accumulation of major symptoms as described above. We now report that two Japanese patients with BBS had normal BUN and creatinine level but elevated levels of cystatin C, a sensitive marker of glomerular filtration rate (GFR).

Patients

A 20-year-old man (patient 1) had mental retardation (minimental state examination 23; normal > 24), rod-cone dystrophy, central obesity (height 158 cm, weight 63 kg, and BMI 25.2) and hypogonadism since the age of 5 years. His waist circumference was 83.5 cm. His blood pressure was 131/85 mmHg, and his heart rate was 61 beats/min. He had normal heart sounds with clear breath sounds. A 16-year-old boy (patient 2), the younger brother of patient 1, had polydactyly in addition to the symptoms described above (height 165 cm, weight 93 kg, and BMI 34.2). His waist circumference was 107 cm. His blood pressure was 128/61 mmHg, and his heart rate was 77 beats/min. He had normal heart sounds with clear breath sounds. Their non-consanguineous parents were apparently healthy. The symptoms of patients and probable autosomal recessive inheritance fulfilled the diagnostic criteria for BBS5. After obtaining informed consent, a DNA chip study was performed at Asper Biotech Ltd. (Tartu, Estonia). The DNA chip (version 5) covered 305 mutations from 14 genes causative for BBS and related diseases (BBS1, BBS2, BBS3, BBS4, BBS5, BBS6, BBS7, BBS8, BBS9, BBS10, BBS12, PHF6, ALMS1, and GNAS1), but identified no pathological alterations. Nevertheless, because about one fifth of patients with clinically definite BBS have no identifiable mutations as described above and because the chip covered only mutations previously reported to be pathogenic, these results could not rule out the possibility of a diagnosis of BBS in our family.

Tests for Renal Morphology and Function, and Other Laboratory Tests

To detect morphological renal abnormalities, the patients underwent abdominal CT scans and abdominal sonography, with no apparent anomalies. Blood and urine tests routinely performed in Japan failed to identify any obvious abnormalities (Table 1, upper rows). Other laboratory data of the elder and younger patients included normal blood sugar levels (78 mg/dl and 81 mg/dl, respectively), normal total cholesterol levels (144 mg/dl and 131 mg/dl, normal 120–220 mg/dl), unelevated triglyceride levels (28 mg/dl and 72 mg/dl, normal 30–150 mg/dl), negative serum CRP, and negative urine occult blood or glucose. Creatinine was measured by an enzymatic method. Serum cystatin C

Table 1. Results of sensitive renal function tests.

Patient #	1	2
BUN (mg/dl)	7	9
Cre (mg/dl)	0.6	0.8
Urine protein	– ~ ±	–
Urine albumin (with cre correction normal = <10)	248*	5.2
Cystation C (0.63–0.95 mg/l)	0.96*	0.97*

Note: *Abnormal values.

and urine albumin were then examined. Cystatin C was measured by a colloidal gold agglutination method. The results showed elevated cystatin C concentrations in both patients and microalbuminuria in the elder patient (Table 1, lower rows). Cystatin C levels of the age- and sex-matched controls were also examined, the result of which showed 0.86 mg/L for an elder control and 0.91 mg/L for a younger control.

Discussion

We describe abnormal levels of serum cystatin C in two patients with BBS (Table 1). Cystatin C is a plasma protein with a molecular weight of 13.4 kDa and belongs to the cysteine protease inhibitors.[8] It is constantly synthesized in all types of cells, excreted into plasma, and filtered completely by the glomeruli. Consequently, increasing serum levels of this marker indicate decreasing GFR. Measurement of cystatin C more sensitively detects mild GFR abnormalities than that of creatinine, a more common but less sensitive marker of GFR,[8] probably because the lower molecular weight of creatinine (113 Da) facilitates its easier filtration in the glomeruli. In addition to the sensitivity, cystatin C is a more reliable marker than creatinine for detection of chronic renal disease, since creatinine levels are affected by many extrarenal patient-related factors such as muscle mass and consumption of cooked meat that is a source of creatinine.[8] Our patients had only mild increases in cystatin C. Nevertheless, because cystatin C levels age-dependently increase with decreasing GFR, the values of our young patients seem sufficiently high for their ages.[8]

A urine albumin level increased only in the elder patient. Patients with BBS occasionally manifest proteinuria,[7] suggesting that patients had not only decreased GFR but also increased protein leakage. Urine albumin is used to detect early phases of diabetic or hypertensive nephropathy.[9] Because neither of our patients showed apparent proteinuria, the elder patient may be in an early phase of protein leakage. In diabetes mellitus, timely treatment with an angiotensin-converting enzyme inhibitor, independently of rise in arterial blood pressure, is considered if improvement of glycaemic control and moderate decrease of dietary protein intake for 6–12 months have failed to reduce the albumin excretion rate.[9] Screening programs for microalbuminuria and early intervention can substantially modify the natural history of diabetic renal involvement and disease and possibly reduce the incidence of end-stage renal failure.[9] In BBS, although such intervention has not been tested yet, we may consider similar protective methods for renal dysfunction.

In conclusion, patients who have BBS with apparently normal kidney functions may have abnormal levels of cystatin C, facilitating an early detection of kidney dysfunctions that might be helpful for prompt correct diagnosis of BBS. However, because our study is based on the results of the small number of patients, conclusion must await further studies.

Acknowledgment

This study was partly supported by the Health and Labour Science Research Grants (Research in intractable diseases) to Drs Hirano, Yamashita, Ikuno, Iwahashi, Ohishi, Mano, and Ishihara.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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