Bardet-Biedl Syndrome with Bronchiectasis: A Rare Association

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Abstract: We are presenting a 16-year-old boy who presented with recurrent respiratory tract infection since childhood with hypogonadism, obesity, dimness of vision and delayed developmental milestones. On further examination, he was found to be a case of Bardet-Biedl syndrome (BBS), a rare genetic disorder with varied presentation associated with bronchiectasis. BBS is diagnosed mainly based on the clinical features developed over time. To the best of our knowledge this is the second case of BBS associated with bronchiectasis.

I. Introduction

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive pleiotropic phenotype genetic disorder. Diagnosis is mainly based on the clinical features. Currently 19 genes are known to be associated with 80% of BBS.¹ The disease frequency is estimated to be 1 per 1,60,000 population in Northern European population and in Arabian population it is estimated to be 1 in 13 500 population due to higher rate of consanguineous marriage.² This syndrome was name after Dr Georges Bardet and Arthur Biedl who described first case in the year 1920.³ BBS is considered to be a ciliary defect where immotile cilia is affected more. Defective immotile cilia is responsible for cystic kidney, retinitis pigmentosa, anosmia, hearing loss, polydactyly and situs inversus.³ Though murine model in BBS had suggested respiratory involvement but bronchiectasis report is extremely rare in human.⁴

II. Case presentation

A 16-year-old Muslim male from West Bengal, India presented with two years history of recurrent productive cough and respiratory distress which was aggravated for last two weeks. He had also history of occasional hemoptysis and fever. He had had history of intermittent oral antibiotic treatment due to lung infection. His mother also complained of delayed developmental milestones including motor, language, and psycho-social milestones. Due to poor performance in the school he was dropped out from the first standard. He had no interest in games, toys and peer group. He only could manage household works. His perinatal period was uneventful and was born vaginally without any complication. He had a history of repeated infection since childhood and was treated with antibiotics. From the three years of age he had visual disturbance which was gradually progressive. His other two siblings were healthy. There was no history of consanguineous marriage of his parents. History of early morning penile tumescence and ejaculation were absent. On examination, he was obese (Body mass index - 31.2 kg/m²; height-143cm, weight-64 kg) with no facial and axillary hair and female type distribution of pubic hair. He had mild pallor, bilateral gynaecomastia and postaxial polydactyly of all four limbs [FIGURE-1]. Blood pressure was 110/80 mm of Hg and pulse was 88/min regular. Respiratory rate was 26/min and temperature was 102°F. On chest auscultation, there was coarse biphasic crepitation in right upper and mid zone with bronchial breath sound with normal vesicular sound on left side. Genital examination revealed small size penis and testicles. [FIGURE-2] Central nervous system examination showed subnormal intelligent quotient (IQ) (IQ-42) and vision was limited to perception of hands movement only though the pupillary light reflex was preserved.

III. Investigations

Ophthalmoscopic Examination: he had waxy disc pallor with bony spicules like structures on both fundus and bilateral peripheral attenuation of retinal vessels consistent with the diagnosis of retinitis pigmentosa. [FIGURE-3]
Laboratory Investigations: Apart from mild pallor all other laboratory reports including oral glucose tolerance tests, liver function tests, renal function tests, thyroid function tests, lipid profile, urine analysis, ultrasonography of abdomen, electrocardiography and echocardiography were normal. Sputum for acid fast bacilli and culture was negative. Chest X-ray and contrast enhanced computed tomography of chest showed consolidation with bronchiectasis noted at right upper lobe, middle lobe and superior segment of right lower lobe. [FIGURE 4 AND 5]. On ultrasonography (USG) of scrotal sac right and left testis were 3x1.7x1.3cm and 3x2.1x1.6cm respectively. USG abdomen and MRI brain was normal. After analysing the clinical features and laboratory investigations we diagnosed him as a case of BBS with right lung bronchiectasis.

IV. Differential Diagnosis

Alström syndrome  
Meckel syndrome  
McKusick-Kaufman syndrome (MKKS)  
Biemond II syndrome  
Prader-Willi syndrome  
Cohen syndrome  
Hurler’s syndrome

V. Treatment

He was admitted and moist oxygen inhalation with bronchodilator therapy (salbutamol and Ipratropium) were started. Intravenous piperacillin and tazobactum (4.5gm thrice daily) with oral azithromycin (500mg once daily) were administered for 10 days. After 10 days of hospitalization patient was discharged with the advice of influenza and pneumococcal vaccination, to maintain adequate hydration, testosterone supplementation, low calorie diet, regular physiotherapy and exercise and ophthalmology follow-up.

VI. Discussion

Modified diagnostic criteria for BBS based on a study conducted in England on 109 BBS patients requires four primary features or three primary plus two secondary features.[Table 1] [5] Due to rarity of disease and varied presentation this disease is typically missed until late adolescent and even upto adulthood. [2] The full spectrum of BBS is found only in 40-45% of cases. [6]
The most common mutation responsible for BBS involves BBS1 (located on chromosome 11q13) and BBS10 (located on chromosome 12q21.2) genes accounting for 23.2% and 20% of cases respectively.[2] Chromosome 3 mutation is responsible for polydactyly and chromosome 15 mutation is associated with morbid obesity. BBS protein encoded by BBS gene are found in basal body and cilia of cells. BBS protein forms ‘BBSome’ which is responsible for trafficking of vesicles to the base of cilia with the help of GDP/GTP exchange factor Rab8 and thus maintaining ciliary function. It is also called as intraflagellar transport (IFT). [7] [8] Abnormality in the ciliary function due to BBS gene defect is the main causative factor for developing variety of phenotypic manifestations. Defect in the IFT of retinal cilia is responsible for death of photoreceptor cells leading to retinal dystrophy. [9] Disruption of Wnt and hedgehog signaling pathways are responsible for obesity and limb malformations respectively.[10, 11] There is also evidence of peripheral leptin resistance which leads to adiposity. [12] Total genetic mutation load across all BBS genes and environmental interaction influence the expressivity of varied disease symptoms. Chromosome and ciliary structure analysis couldn’t be performed in our case. Though the motile cilia is relatively spared in BBS, increased prevalence of respiratory distress syndrome (RDS) (12%), otitis media (33%), rhinitis (36%) and asthma (21%) have been reported.[4] But the incidence of these disorders in BBS are far less than in primary ciliary dyskinesia (PCD) which specifically involves motile cilia. PCD associated with retinitis pigmentosa and bronchiectasis is not so scarce.[13, 14] But bronchiectasis associated with BBS is extremely rare. To the best of our knowledge only one case of BBS with bronchiectasis had been reported so far in literature. [15]

There is currently no known curative specific therapy except managing complications. In this case bronchiectasis was managed with antibiotics and maintenance of bronchial hygiene.

VII. Conclusion

BBS presents with multitude of symptoms. Symptoms may develop simultaneously or develop over time. To diagnose early, respiratory symptoms in patients with diminished vision or hypogonadism should raise the suspicion of BBS associated with bronchiectasis. Bronchiectasis needs to be managed with maintenance of bronchial hygiene, antibiotics and bronchodilator therapy.
Bardet-Biedl Syndrome With Bronchiectasis: A Rare Association

References

Table 1: Diagnostic Criteria Which Are Present In Our Patient

<table>
<thead>
<tr>
<th>Primary Features</th>
<th>Frequency Of Association</th>
<th>In Our Patient</th>
</tr>
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<tbody>
<tr>
<td>Rod-Cont Dystrophy</td>
<td>&gt;90%</td>
<td>Present</td>
</tr>
<tr>
<td>Male Hypogonadotropic Hypogonadism</td>
<td>88%</td>
<td>Present</td>
</tr>
<tr>
<td>Obesity</td>
<td>72%-96%</td>
<td>Present</td>
</tr>
<tr>
<td>Postaxial Polydactyly</td>
<td>21%-69%</td>
<td>Present</td>
</tr>
<tr>
<td>Learning Disabilities</td>
<td>62%</td>
<td>Present</td>
</tr>
<tr>
<td>Renal Anomalies</td>
<td>53%-63%</td>
<td>Not Present</td>
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<tr>
<td>Secondary Features</td>
<td></td>
<td></td>
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<tr>
<td>Speech Disorder Delay</td>
<td>47%</td>
<td>Present</td>
</tr>
<tr>
<td>Syndromal Cataract/Astegnation</td>
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<td></td>
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<tr>
<td>Brachydactyly Syndacty</td>
<td></td>
<td></td>
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<tr>
<td>Developmental Delay</td>
<td>50%</td>
<td>Present</td>
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<tr>
<td>Polyuria/Polydipsia (Nephrogenic Diabetes Insipidus)</td>
<td>33%</td>
<td>Not Present</td>
</tr>
<tr>
<td>Ataxia Poor Coordination/Inbalance</td>
<td>40%</td>
<td>Not Present</td>
</tr>
<tr>
<td>Mild Spasticity (Especially Lower Limbs)</td>
<td></td>
<td>Not Present</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>45%</td>
<td>Not Present</td>
</tr>
<tr>
<td>Dental Crowding/Hypodontia/Small Roots/High Arched Palate</td>
<td>27%</td>
<td>Not Present</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy/Coarctal Heart Disease</td>
<td>7%</td>
<td>Not Present</td>
</tr>
<tr>
<td>Hepatic Fibrosis</td>
<td></td>
<td>Not Present</td>
</tr>
</tbody>
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