NOTE

Bartter’s Syndrome Associated with Indirect Hyperbilirubinemia: A Possible Clinical Variety

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Abstract

This report deals with three cases of Bartter’s syndrome whose symptomatology was associated with indirect hyperbilirubinemia. The bilirubin disorder was suggestive of Gilbert’s syndrome, with no pathological findings being detected as far as the liver function was concerned. Furthermore, the unconjugated fraction of bilirubin increased after fasting. The therapy with indomethacin exerted beneficial effects on both electrolytes and bilirubin disorders, and the patients recovered a good healthy state. These findings suggest the possibility that Bartter’s syndrome may coexist in a variety associated with indirect hyperbilirubinemia.

Bartter’s syndrome is a quite rare disease characterized by hypokalemia and metabolic alkalosis associated with high levels of plasma renin activity and aldosterone in the absence of high blood pressure (BP). Since its initial description in 1962 (Bartter et al.), a certain number of reports have attracted medical attention regarding certain anomalous aspects of the disease, either clinical or biochemical (Fanconi et al., 1971, Erkens et al., 1973, Meyer et al., 1975, 1978, Bartter, 1981, Mattioli et al., 1984, Gill, 1985, Jest, et al., 1989).

The present paper deals with three cases of Bartter’s syndrome, whose clinical abnormality was the simultaneous occurrence of mild jaundice. The hyperbilirubinemic state was attributable to an increase in the indirect fraction of bilirubin as it occurs in Gilbert’s syndrome (Gilbert et al., 1907, Whitmer et al., 1983). It is postulated that the occurrence of one variety of Bartter’s syndrome may be associated with indirect hyperbilirubinemia.

Methods

Plasma(P) and urinary(U) sodium(Na), potassium(K) and chloride(Cl) concentrations were measured by flame photometry. Plasma renin Activity (PRA), plasma aldosterone (PA), and
urinary aldosterone (UA) were determined by RIA methods of Haber et al. (1969), and McKenzie and Clements (1974), respectively. Plasma cortisol (PC) was assayed by the method of Ruder et al. (1972). Plasma adrenocorticotropic hormone (ACTH) was measured by RIA using a commercial kit by SORIN, Saluggia, Vercelli, Italy. Urinary 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) were measured by the colorimetric method of Porter and Silber (1954), and Drekter et al. (1947), respectively. Serum bilirubin (BI) was determined by spectrophotometry. For habitual Na (120-140 mEq/24-h) intake, the normal values were as follows: PNa 135-145 mEq/l; PK 3.7-5.2 mEq/l; PC1 100-105 mEq/l; UNa 85-115 mEq/24-h; UK 40-55 mEq/24-h; UCl 75-100 mEq/24-h; supine PRA 0.8-1.5 ng/ml/h; upright PRA 1.5-4.7 ng/ml/h; supine PA 2.2-14.0 ng/dl; upright PA 10.0-35.0 ng/dl; UA 5-25 µg/24-h. For regular caloric intake, the normal values for BI were as follows: total (T) BI 0.40-1.00 mg/dl; indirect (I) BI 0.30-0.80 mg/dl; direct (D) BI 0.10-0.20 mg/dl.

Case Reports

Case 1.
This patient, a 24 year-old white woman, was admitted to the hospital because of clinical symptoms characterized by muscular weakness from which she had been complaining for at least 2 years. The family pedigree was negative. The personal history was positive for episodes of jaundice that were concurrent with the beginning of muscular fatigueability. She was investigated from a physical and biochemical point of view. She was found to be normotensive (BP 120/75 mmHg). Scleral jaundice was observed. Both severe hypokalemia (PK 3.7-5.2 mEq/l) and metabolic alkalosis (pH 7.43; HCO3 28 mEq/l) were detected. TBI was found to increase due to an increase in its indirect fraction (TBI 1.66 mg/dl; IBI 1.50 mg/dl; DBI 0.16 mg/dl). After fasting, hyperbilirubinemia increased by about 100% in its indirect aliquot as it occurs in Gilbert’s syndrome. PRA and PA, and UA were found to have increased (supine PRA 8.8 ng/ml/h, upright PRA 12.1 ng/ml/h; supine PA 15.7 ng/dl, upright PA 40.0 ng/dl, UA 35 µg/24-h). UK was also found to have increased (75 mEq/24-h) along with UCl (115 mEq/24-h). PC (12.0 µg/dl) and ACTH (45 pg/dl) were found to be normal along with 17-OHCS (5.4 mg/24-h) and 17-KS (10.0 mg/24-h).

Liver and kidney functions were carefully investigated by means of instrumental and laboratory studies. No additional morpho-functional disorders were documented. The patient was treated with indomethacin (25 mg, orally, twice a day). The symptoms disappeared after a few days, along with the hypokalemia and metabolic alkalosis. PRA, PA and UA returned to normal values. The hyperbilirubinemia substantially normalized. Because of the sensitivity to indomethacin the patient was diagnosed to be affected with Bartter’s syndrome associated with Gilbert’s syndrome. Liver and kidney biopsy was not performed as ethical reasons prevent such an invasive maneuver if the diagnosis can be made on a clinical basis.

Case 2.
This patient was a 28-year-old white man who was hospitalized because of intermittent episodes of scleral jaundice associated with severe asthenia, muscular tremors having initiated some 48 months prior. His family history was negative, as was his clinical past. On physical examination, he showed a clear jaundice of the mucosae and skin, but no other pathological signs. His blood pressure was 115/70 mmHg, urine was red in color and feces was hyperchromic. Instrumental exploration, including echography of liver and kidneys, and pyelography, showed completely negative. Laboratory data for hepatic and renal function were substantially normal. However, the bilirubin was found to have abnormally increased (TBI 5.20 mg/dl, IBI
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4.60 mg/dl, DBI 0.60 mg/dl), while serum potassium was seen to be substantially reduced (PK 2.4 mEq/l). Arterial pH (7.46) was alkalotic because of a bicarbonate excess (HCO3 27.8 mEq/l). UK (53 mEq/24-h) and UCl (120 mEq/24-h) were found to be excreted in large amounts. PRA, PA and UA were seen to be markedly increased (supine PRA 18 ng/ml/h; upright PRA 21 ng/ml/h; supine PA 12.2 ng/dl; upright PR 12.2 ng/dl; upright PA 25.6 ng/dl; UA 45 μg/24-h), but PC (14 μg/dl) and ACTH (65 pg/ml) were normal. The fasting test was positive in the sense that the bilirubin increased to about twice its baseline values (TBI 9.10 mg/dl; IBI 8.70 mg/dl; DBI 0.40 mg/dl). A diagnosis of Bartter's syndrome associated with Gilbert's syndrome was made. The diagnostic confirmation was obtained by treatment with indomethacin (25 mg, orally, twice a day). After one week of therapy, the laboratory data showed a consistent normalization: TBI 1.10 mg/dl; IBI 0.7 mg/dl; DBI 0.4 mg/dl; PK 4.3 mg/dl; pH 7.4; HCO3 26.0 mEq/l; supine PRA 1.1 ng/ml/h; upright PRA 2.1 ng/ml/h; supine PA 8.0 ng/dl; upright PA 14.0 ng/dl; UA 15 μg/24-h. Due to the successful clinical diagnosis, a biopsy of liver and kidney was not performed.

Case 3.

This patient was a 25-year-old white woman who was clinically investigated due to symptoms characterized by fatiguability, muscular weakness, tachycardia and episodes of recurrent jaundice. The symptoms had continued for at least 7 years. On admission, the patient was normotensive (BP 110/70 mmHg) and showed a scleral jaundice. The urine was palm in color and the feces was hyperchromic. Laboratory data showed hypokalemia (PK 2.1 mEq/l) associated with metabolic alkalosis (PH 7.47; HCO3 29.7 mEq/l). A great amount of UK (74.1 mEq/24-h) and UCl (112 mEq/24-h) was excreted. PRA, PA, and UA were found to be above the normal limits (supine PRA 10.0 ng/ml/h; upright PRA 12.0 ng/ml/h; supine PA 20 ng/dl; upright PA 50.0 ng/dl; UA 33.4 μg/24-h). PC (20.0 μg/dl) and ACTH (35 pg/dl) were found to be normal. BI was found to have abnormally increased (TBI 2.6 mg/dl; IBI 0.11 mg/dl). Other laboratory data for hepatic and renal functions were substantially normal. Both the roentgenographic and echographic findings were normal. The fasting test was positive as bilirubin increased more than 100% from the control values (TBI 5.20 mg/dl; IBI 5.05 mg/dl; DBI 0.15 mg/dl).

The diagnosis of Bartter's syndrome associated with Gilbert's syndrome was provisionally made and confirmed by the administration of indomethacin (25 mg, orally, twice a day). During this therapy, both the clinical and laboratory findings demonstrated a return to physiological values (PK 4.1 mEq/l; pH 7.41; HCO3 25.7 mEq/l; supine PRA 1.45 ng/ml/h; upright PRA 2.1 ng/ml/h; supine PA 10.5 ng/dl; upright PA 17.0 ng/dl; UA 6.36 μg/24-h; TBI 0.5 mg/dl; IBI 0.39 mg/dl; DBI 0.11 mg/dl). The patient was not considered for a biopsy of the liver and kidney because of the adequate clinical diagnosis.

Discussion

This report presented three clinical cases which were substantially identical in both their symptomatology and laboratory aspects. None of them either factitiously or surreptitiously used substances that could cause a pseudo-Bartter's syndrome (Rosenstein et al., 1977, Romos et al., 1980, Robb et al., 1984). Nevertheless, all of them were suffering from muscular disturbances associated with a consistent high urinary excretion of potassium and hypochloremic hypokalemia as well as metabolic alkalosis.
It is important to note that they were all normotensive and showed a substantial increase in plasma renin activity and plasma aldosterone. Kidney biopsies were not performed as ethical reasons prevent an invasive maneuver. A lack of hypertrophy of the juxtaglomerular apparatus has occasionally been documented (Kornerup et al., 1978, Bettinelli et al., 1980, Barakat et al., 1981). The diagnosis of Bartter's syndrome was presumed and later confirmed when therapeutic treatment with indomethacin caused the disappearance of clinical symptoms and normalization of laboratory data (Richards et al., 1978, Vierhapper et al., 1980, Güllner et al., 1977, Sasaki et al., 1980).

The scientific interest in these cases is mainly due to the fact that the patients showed a concomitant disorder in the bilirubin metabolism. All of them suffered from recurrent episodes of jaundice that were sustained by an increase in the unconjugated fraction of bilirubin, without any demonstrable pathology of the liver. In each of them, the indirect bilirubin increased after food restriction showing the typical response of Gilbert's syndrome (Bloomer et al., 1971, Gollan et al., 1976, Whitmer et al., 1983).

A clinical point of interest arose due to the finding that the therapy with indomethacin was seen to improve not only the pathological indices of Bartter's syndrome, but also the episodes of jaundice. Taking into consideration both the combined onset of symptomatology and the joint response to indomethacin, it was reasonably concluded that in these cases there was a relationship between the mechanism responsible for the disturbance of electrolyte balance and renin-angiotensin-aldosterone system on the one hand, and the disturbance of bilirubin metabolism on the other hand. Therefore, the possible role of alkalosis as a cause in reversing the BI transport across membrane can be discounted, as demonstrated in the clinical studies (Sawitsky et al., 1968, Hodr et al., 1982).

As the full recovery of all clinical and biochemical disorders was obtained by the use of indomethacin, it was postulated that the prostanoid system might be the common pathway to explain such a clinical picture. Unfortunately, our conclusions are still only speculative, since the clinical nature of this study could not permit us to clearly identify the common denominator underlying the pathogenesis. Furthermore, while the literature has provided convincing evidence that prostaglandins play a pathogenetic role in the biochemical disorders of Bartter's syndrome (Verberkmoes et al., 1976, Bardgett et al., 1978, Bartter, 1981, Boden et al., 1978, Sasaki et al., 1980. Dunn, 1981), there is still no documentation existing on the role of prostaglandins in the bilirubin metabolism (Jansen et al., 1988). Owing to such a present lack of knowledge, the clinical cases presented herein will remain merely descriptive, suggesting the possibility that Bartter's syndrome may show itself in a variety that can be associated with indirect hyperbilirubinemia.

References


