Gitelman’s Syndrome and Hypomagnesemia

Key words: Gitelman’s syndrome, thiazide sensitive Na/Cl cotransporter, Bartter’s syndrome

In this issue of “Internal Medicine”, an interesting case report regarding the psychological symptoms in Gitelman’s syndrome is presented (1) and this case is suitable to understand the current knowledge about Gitelman’s syndrome.

Gitelman’s syndrome was first reported by Gitelman et al in 1966 as a variant of Bartter’s syndrome (2). Gitelman’s syndrome has characteristics common to Bartter’s syndrome, such as salt wasting, hypokalemia, and metabolic alkalosis. Elevated plasma renin activity and aldosterone levels are well-known abnormalities in both Bartter’s and Gitelman’s syndrome, although these changes are thought to be induced as the secondary changes following by salt wasting. In comparison with Bartter’s syndrome, Gitelman’s syndrome has two distinct features, hypocalciuria and hypomagnesemia. Onset of the symptoms is also different between Gitelman’s and Bartter’s syndrome. In general, symptoms including general fatigue, tetany, and muscle weakness, occurs during adolescence in Gitelman’s syndrome, while the patients with Bartter’s syndrome show symptoms, mainly dehydration, right after the birth. This case was diagnosed as Gitelman’s syndrome at a rather unusually old age, while she showed characteristic features of this syndrome; hypomagnesemia, hypokalemia, and hypocalciuria. Gene analysis confirmed the diagnosis of Gitelman’s syndrome and mutated site of SLC12A3, thiazide-sensitive Na/Cl-cotransporter gene, was identical to the mutation reported by Simon et al (3). This case report provides important information regarding Gitelman’s syndrome. Firstly, the clinical characteristics of this case are consistent with typical Gitelman’s syndrome and it is very informative to learn about this syndrome. Hypokalemia is prominent, and hypomagnesemia and hypocalciuria are also evident. In spite of these abnormalities, this case had not been diagnosed as this syndrome by the age of 69. Functional test with furosemide and thiazide strengthened the diagnosis, but the final diagnosis was made after obtaining the results of gene analysis. These step by step diagnostic procedures are recommended for the differential diagnosis with hypokalemia. The first step should be the precise evaluation of blood and urine biochemical data, and the next step, functional examination. The last and most confirmative step is the determination of gene mutation. Renal biopsy to confirm hyperplasia of juxtaglomerular apparatus is not necessary any more to diagnose this syndrome.

On the other hand, this case presented one unique clinical symptom, depression, which was readily improved by magnesium infusion. In various hereditary diseases with hypomagnesemia, neuromuscular symptoms are very common, including tetany, muscle clamp, and seizures (4). In some diseases, untreated patients with hypomagnesemia show mental retardation. Among these patients and our cases (5), however, the depressive state has never been described. This fact does not eliminate the notion that the depressive state and hypomagnesemia are directly linked. In fact, not only hypomagnesemia but also hypocalcemia and various electrolyte disturbances are known to induce alterations in the central nervous system. With careful observation of Gitelman’s patients, it is possible that we may discover more patients with depression and other psychological abnormalities.

Another suggestive finding in this case report is that this case did not develop renal failure even without treatment for hypokalemia by the age of 59. In a previous paper, it was reported that some patients developed end-stage renal failure by hypokalemia. It is possible that mild hypokalemia in Gitelman’s syndrome in comparison with Bartter’s syndrome does not necessarily induce severe renal impairment. Indeed, none of the 20 patients, who are visiting or were referred to our clinic, did not have accompanying renal impairment. These findings strongly suggest that Gitelman’s syndrome has a much better prognosis than Bartter’s syndrome regarding renal function.

One important unresolved question about Gitelman’s syndrome is the cause of hypomagnesemia. It is well established that this syndrome is caused by mutation of thiazide-sensitive Na/Cl-cotransporter, as described above. With genetical analysis of the patients and the development in molecular biology, most of the features in Gitelman’s syndrome are explained by the loss of function of this cotransporter in the distal convoluted tubules. Hypocalciuria is explained by the enhanced uptake of calcium by the distal convoluted tubular cells due to decreased cation transport via apical membrane in these cells. Hypokalemia is also explained by impaired sodium reabsorption by distal convoluted tubules and resultant sodium loading to the cortical collecting ducts. In contrast to these features, the hypomagnesemia in Gitelman’s syndrome is still a mystery in this syndrome. In the normal kidney, magnesium is reabsorbed mainly by the thick ascending limbs of Henle, which is impaired in
Bartter’s syndrome but not in Gitelman’s syndrome, while hypomagnesemia is not seen in Bartter’s syndrome. Recently, several proteins related to magnesium reabsorption have been cloned. Currently, the relationship between those proteins and the thiazide-sensitive Na/Cl-cotransporter are not known. Likely in the near future, the pathophysiological roles of those proteins in Gitelman’s syndrome will be elucidated.

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References