To the Editor:

Manoharan\(^1\) reported on family cases of low serum haptoglobin (Hp) concentration (hypohaptoglobinemia). In this letter, it was postulated that they were cases of congenital Hp deficiency (anhaptoglobinemia), which the author described as an entity that has received little recognition in literature. However, epidemiological studies have found numerous cases of anhaptoglobinemia all over the world in the last four decades.\(^5\) In true “anhaptoglobinemia” (Hp 0-0 phenotype), the expression of the Hp gene is absent.\(^7\) This condition is present in approximately 1 of every 1,000 whites.\(^2\) In Melbourne (Australia), 1.7% of the population carries the Hp 0-0 phenotype.\(^1\) In blacks, especially of West African origin (Nigeria, Cameroon), anhaptoglobinemia is more frequent (greater than 30%).\(^1\) The frequency of Hp 0-0 among blacks in the United States is 4%.\(^3\) An increase in the prevalence of anhaptoglobinemia has also been reported among the white elderly population.\(^2\)

Manoharan\(^1\) further speculated about the inheritance of this condition. Also, this subject has been studied in detail in literature.\(^6,7\) Primary anhaptoglobinemia has been reported to occur in families carrying a “silent allele” (Hp 0) with no gene product.\(^6,7\) These family studies do not support a dominant type of inheritance.\(^6,7\) Next to the occurrence of Hp 0-0, secondary familial hypohaptoglobinemia can occur as a consequence of congenital diseases such as hemolytic disorders (eg, hereditary red cell membrane and enzyme defects, thalassemia, sickle cell anemia).\(^7\) After destruction of erythrocytes, Hp is saturated when approximately 500 to 1,500 mg/L of free hemoglobin is released into the plasma, which corresponds to only a moderate degree of hemolysis.\(^2\) In view of the relatively low hemoglobin-binding capacity of Hp, even common lifestyle factors (eg, repetitive physical exercise associated with limited mechanical trauma to erythrocytes) may induce relative hypohaptoglobinemia.\(^2\)

Difference between congenital and acquired hypohaptoglobinemia can simply be made by an additional determination of serum hemopexin in serum.\(^2,8\) Hemopexin binds free heme.\(^8\) After saturation of the hemoglobin-binding capacity of Hp, serum hemopexin levels start to decrease, whereas the Hp concentration remains at low level (less than 0.3 g/L). During intense hemolytic processes or in chronic hemolytic diseases, determination of serum hemopexin should be performed.\(^2,8\) In the case of an Hp 0-0 phenotype without hemolysis, hemopexin levels will remain unchanged.

A critical point in the diagnosis of hypohaptoglobinemia is the age dependency of the expression of the haptoglobin gene in infants. In neonatal serum, no Hp can be detected.\(^9\) The protein is detectable in less than 50% of children between the ages of 1 and 2 months.\(^9\) At the sixth month, failure to detect Hp becomes relatively rare in whites.

Another difficulty in interpreting low serum haptoglobin levels is the fact that its reference values depend on the Hp phenotype.\(^2\) The reference values for Hp 2-2 in serum are considerably lower (0.38 to 1.50 g/L) than for Hp 2-1 (0.44 to 1.83 g/L) and Hp 1-1 (0.57 to 2.27 g/L).\(^2\) Therefore, Hp 2-2 subjects (30% to 50% of whites) may be in a state of relative hypohaptoglobinemia compared with the other phenotype. To illustrate this, we performed a careful re-investigation of 10 serum samples with hypohaptoglobinemia (less than 0.3 g/L) and found no detectable trace of Hp on electrophoresis. Gel permeation chromatography of these sera (based on differences in molecular mass between the Hp phenotypes) demonstrated six cases of Hp 2-2, one case of Hp 2-1, and only three cases of “true” anhaptoglobinemia.

In conclusion, congenital anhaptoglobinemia cannot be regarded as a rare phenomenon and should be distinguished from secondary hypohaptoglobinemia by additional determination of serum hemopexin concentration. Furthermore, hypohaptoglobinemia has important clinical consequences: this condition is associated with heme iron accumulation due to a less efficient clearance of free hemoglobin in body fluids, resulting in iron-driven oxidative stress and vitamin C depletion.\(^10-11\)

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REFERENCES
Congenital Anhaptoglobinemia Versus Acquired Hypohaptoglobinemia

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