Spinal Cord Disease in Hereditary Spherocytosis: Report of Two Cases With a Hypothesized Common Mechanism for Neurologic and Red Cell Abnormalities

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Two unrelated patients with hereditary spherocytosis developed idiopathic spinal cord dysfunction. This coincidence, combined with similar individual case reports in the older European literature, suggests that abnormalities may exist in constituents common to red cell membranes and nerve tissue. A similar conclusion has been proposed to explain red cell membrane abnormalities in some of the muscular dystrophies.

CONSIDERABLE EVIDENCE has accumulated that a defect in the red cell membrane underlies the shortened survival of erythrocytes in hereditary spherocytosis. Most recently, attention has centered on membrane proteins as possibly mutant, or otherwise abnormal, in this disease. One such protein, termed spectrin, polymerizes into fibers and appears as a network of filamentous structures at the inner (cytoplasmic) aspect of the red cell membrane. Various data suggest that it may be critical to normal red cell shape and deformability. This protein (as well as many other proteins which polymerize into filamentous or tubular structures, as for instance in cilia, mitotic spindles, and neurofilaments) is precipitated by drugs such as vinblastine. When normal red cells are treated with these drugs, they become morphologically similar to hereditary spherocytes; their osmotic fragility and sodium permeability are increased, and the cells are specifically removed from the circulation by the spleen. These abnormalities are identical to those of hereditary spherocytosis (HS) red cells and support the hypothesis that abnormalities in spectrin or other fibrous proteins of the red cell membrane might underlie this disorder. Further evidence derives from experiments in which red cells are heated in calorimeters. At exactly 50°C, spectrin denatures solely with associated formation of microspherocytes. These heat-induced spherocytes, when reinjected into the circulation, are specifically sequestered and destroyed in the spleen, as are hereditary spherocytes.

Since it seems possible in HS that abnormalities in membrane fibrous protein might not occur exclusively in red cells but might affect other tissues as well, we view as particularly interesting two HS patients seen at this hospital who have manifested neurologic diseases of unknown cause. Our interest has been especially provoked because nerve tissue is an extremely rich source of vinblastine-
reactive fibrous proteins. These proteins appear as neurofilaments and neurotubules, and it has been presumed that vinblastine and especially its analogue, vincristine, produce neurotoxicity when used as chemotherapeutic agents because of their ability to react with these proteins. The finding of late-onset, idiopathic spinal cord dysfunction in the two unrelated patients with HS to be described, suggests that a common biochemical error might underlie both red cell and neurologic defects in this syndrome. Although to our knowledge no previous reports of such coincidence has appeared in the American or English literature, isolated case reports of probable HS associated with various neurologic, especially spinal cord, diseases have appeared since 1914 in the European literature.

CASE REPORTS

Case 1

H.F., a 51-yr-old man, was referred to the University of Minnesota Hospital following the discovery of hereditary spherocytosis in his 25-yr-old daughter. He had noted transient episodes of jaundice in childhood and a cholecystectomy was required at age 44 for cholecystitis and cholelithiasis. Two years prior to admission, indolent skin ulcerations over the left medial malleolus became evident, and splenomegaly was noted for the first time. Apart from his daughter, no family member had symptoms suggesting HS. Upon admission to hospital for workup of hemolytic disease and possible splenectomy, a history of slowly progressive neurologic dysfunction was elicited. He complained of increasing left-sided weakness and loss of balance during the previous 5 yr., and several attacks of urinary incontinence had been noted during the previous year. Physical examination revealed an enlarged spleen, palpable 4 cm beneath the left costal margin. The neurological examination was consistently abnormal with excessively hyperactive, but symmetrical, deep tendon reflexes. Babinski's sign and sustained ankle clonus were present bilaterally. Moderate weakness of the left hip musculature was noted, and heel-to-knee coordination was impaired bilaterally. The gait was unsteady, and Romberg's sign was present. Position sense of the toes was impaired, especially on the left side, although vibration sense was normal. Sharp/dull sensation on the medial aspects of both legs was poor.

Laboratory investigation documented a reasonably well-compensated hemolytic anemia, with PCV = 0.37 and reticulocyte count of 5.4%. Leukocyte and platelet counts were normal, as were blood electrolytes and liver function tests. Both direct and indirect Coombs' tests using several (anti-IgG, IgM, IgA, and complement) antisera were negative. The blood smear showed many microspherocytes and marked polychromatophilia. Following incubation for 24 hr without glucose, the osmotic fragility of the red cells was markedly increased; 50% of the red cells were hemolyzed at a concentration of 0.58 g/dl NaCl (control 50% hemolysis at 0.51 g/dl NaCl), and hemolysis was first perceived at 0.8 g/dl NaCl (control at 0.6 g/dl). Serum folate and vitamin B12 levels were normal (6.0 µg/liter and 475 ng/liter, respectively), and a Schilling test produced a normal urinary radioactive vitamin B12 excretion of 25% in 24 hr. The spinal fluid, which was under normal pressure, contained no cells, had a normal glucose and protein content, and generated a normal colloidal gold pattern. Myelography demonstrated no extrinsic lesions, and electromyography revealed no evidence of lower motor neuron lesions. Screening of urine for heavy metals was negative.

The diagnosis of HS was supported by family history, blood smear, osmotic fragility studies, and the physical findings of leg ulceration and splenomegaly. The neurologic findings were diagnosed by neurology consultants as an "idiopathic degenerative demyelinating process of the spinal cord." Prior to splenectomy, routine preoperative hemostasis screening revealed a striking reduction in platelet adhesiveness to glass beads (4% compared to a normal range of 25%-65%), and deficient primary and secondary aggregation responses of platelets to epinephrine at a concentration of 6.875 x 10^{-5} M. Nevertheless, splenectomy was performed without complication, and all evidence of hemolysis subsequently disappeared. Three years following splenectomy, neurologic function has only slightly worsened, although the patient now complains of impotence.
The patient's daughter, who had also had a splenectomy, showed no evidence of neurological dysfunction (or of hemolysis).

Case 2

V. M., a 72-yr-old white female, was admitted to the University of Minnesota Hospital complaining of a slowly progressive weakness in her right hand and left leg over the preceding 2 yr. The weakness of her leg had progressed so that walking required the support of a cane. Six years previously a cholecystectomy had been performed for cholelithiasis, and the patient had been told on multiple previous occasions that she had "chronic anemia." One son and two daughters of the patient have HS; both daughters have children with HS—all verified in our laboratory. The patient's son and one daughter have been splenectomized, with subsequent cessation of hemolysis. None of these family members has any neurologic dysfunction. The patient has otherwise been well except for intermittent episodes of palpitation over a 25-yr period which has required cardioversion on one occasion. Abnormalities on physical examination included a spleen tip which was palpable 3 cm below the left costal margin and a II/VI systolic ejection murmur at the base of the heart. The neurologic examination was distinctly abnormal, with evident spasticity of both lower extremities. The deep tendon reflexes were hyperactive without sustained clonus, and a moderate reduction in motor function was noted in both the lower and the right upper extremities. Vibratory sense was intact, but position sense was abnormal; an extensor plantar response was elicited on the right side. A right-sided upper extremity intention tremor and a broad-based gait were also apparent.

Laboratory examination revealed a moderate hemolytic anemia with PCV = 0.27 and reticulocyte count of 6%. Peripheral blood smears revealed numerous microspherocytes and polychromatophilia. Osmotic fragility of red cells was markedly increased following incubation for 24 hr; 50% hemolysis occurred at an NaCl concentration of 0.66 g/dl, and first perceptible hemolysis occurred at 0.8 g/dl. Leukocyte and platelet counts were normal. The serum vitamin B12 was 335 ng/liter, and a Schilling test revealed normal B12 absorption. Coombs' tests using several antisera were negative. Spinal fluid examination, myelography, electromyography, and a brain scan were normal. Neurology consultants diagnosed the patient as suffering from an "idiopathic spinal cord degenerative process."

In addition to the hematologic and neurologic diseases, the patient manifested on numerous electrocardiographs transient and varying supraventricular arrhythmias, which were diagnosed as "sick sinus syndrome." (Serum thyroxine levels were consistently normal.)

A diagnosis of HS was made on the basis of family history, red cell morphology, osmotic fragility studies, and splenomegaly. Splenectomy was deemed unwise because of her age and cardiovascular problems. The neurologic findings have slowly but definitely progressed over the past 1½ yr, while her hemolytic anemia continues with fair compensation on folic acid therapy.

DISCUSSION

As recently reviewed in a textbook on neurologic symptoms in blood diseases, the older European medical literature contains a few individual case reports of central nervous system dysfunction in "constitutional hemolytic icterus"—a term generally used for hereditary spherocytosis in the older literature. Separate reports of "spastic paraplegia," "Strumpell-Lorraine paraplegia," "funnicular changes," "Friedreich's disease," "P. Marie's ataxia," "myoclonic epilepsy with ataxia syndrome and cerebellar disturbances," "muscle atrophy," and "tabes-like syndrome" have all appeared. The nervous system abnormalities were noted in patients of varying ages (9–42 yr) and did not appear to worsen systematically with age. To our knowledge, the association of spinal cord degeneration with HS, as represented by our two cases, has not previously been emphasized in the American literature. Since recognizing these two patients, we have carefully assessed the neurologic status of 15 other
HS patients seen at our institution (including family members of the propositi); no additional neurologic disorders have been uncovered.

If, as seems likely, an abnormal structural protein of the red cell membrane produces the error in HS red cells, a careful search for abnormalities in other tissues might be productive. In fact, Dacie, in an extensive compilation of possible associated disorders in HS patients, described defects in ocular lenses and the skeleton in several such patients. Although it is possible that these disorders might reflect a second genetic abnormality closely linked to HS, we believe it is not fortuitous that neurologic dysfunction has occurred in this disease as well. Nerve tissue is particularly abundant in fibrous proteins that react with vinblastine (and colchicine). In fact, precipitation by vinblastine has been utilized to purify these proteins—"tubulins"—from brain and spinal cord. Although there are no comparative chemical or physical data on spectrin, brain tubulin, or other fibrous proteins, the fact that vinblastine, when added to normal red cells, produces all the typical characteristics of hereditary spherocytes tempts us to speculate that a prototype protein of similar or identical composition exists in red cell membranes and nerve cell tissue. If so, we suggest that these proteins may share a common abnormality, resulting in the concurrence of hereditary spherocytosis and long tract degenerative disease in these two patients. We would emphasize that HS is very likely a syndrome reflecting several diverse mutations in red cell membrane proteins; thus, the type of neurologic involvement described herein might only be expected with certain of these mutations.

Regarding our attempt to relate neurologic and red cell abnormalities, we find particularly interesting a recent report of red cell surface abnormalities in at least two types of muscular dystrophy. Even more provocative in this regard are recent studies by Roses and Appel. These authors have demonstrated that in myotonic muscular dystrophy, red cell membrane proteins are abnormally phosphorylated by endogenous protein kinase; intriguingly, this same phosphorylation has recently been shown to be deficient in HS red cell membranes by Greenquist and Shohet, as well as by ourselves.

In a similar vein, we note that platelets are also particularly rich in vinblastine-reactive microtubules; disruption of these structures with the drug produces defects in platelet adhesiveness and aggregation, similar to those noted in case 1. We have observed and will subsequently report on two other patients with hereditary spherocytosis manifesting defects in platelet function identical to those of case 1. From such associations, we feel it likely that, as the underlying defects in HS red cells are more clearly elucidated, increasing numbers of abnormalities in other tissues will become perceptible and probably will be understood in biochemical terms, rather than being assumed to represent fortuitous coincidences.

REFERENCES

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SR McCann and HS Jacob