The first identified case of thalassemia?

The spread of thalassemia among prehistoric populations of the Mediterranean basin has been linked to the increased risk to early agriculturalists posed by the *Plasmodium falciparum* parasite. We here present the earliest case, to our knowledge, of thalassemia diagnosed on the basis of long bone remains. We further discuss the value of this finding for our understanding of the transition from foraging to agriculture.

Introduction

Thalassemia, an inherited abnormality, is a type of hemolytic anemia caused by the deficiency of a particular hemoglobin protein (Harris, 1980). There are two major and several intermediate and minor forms of the disease. In the classical type, affecting mainly central and eastern Mediterranean populations (e.g. Italians, Greeks), the beta chain of the globulin molecule is involved. In other areas of the world, mainly southeast and east Asia (e.g. India, China), both the beta and alpha chains are implicated.

Homozygous thalassemia major (or Cooley’s anemia) carries a very high mortality rate in infants and children, and even when the individual survives, life expectancy is short. However, heterozygotes with intermediate and minor forms of the disease usually survive into adulthood, and have a selective advantage over non-carriers in malaria-infested areas because of the malaria parasites’ inability to utilize the affected red cells (Allison, 1955; Gloria-Bottini et al. 1980).

Thalassemia major and intermediate forms of the disease usually manifest skeletal changes. Most minor variants do not (Ortner & Putschar, 1981).

The origin of thalassemia in the eastern Mediterranean region is still unclear. Gatto (1948, 1960) claimed that thalassemia was already present in the early paleo-insular populations of Sicily during the Upper Palaeolithic period. This view, however, was criticized by Maxia & Cossu (1950) and later by Ascenzi & Balistreri (1977), who found no real evidence of the disease in skeletal material from the «Cave of San Teodoro» (on which Gatto based his conclusions). The fact that the present incidence of thalassemia is highest in the areas where ancient Greek immigration was most intense (e.g. Sicily, Sardinia) led Silvestroni et al. (1952) to suggest that thalassemia originated in Greece and spread to Italy when the latter was colonized by the Greeks in the 8th-6th centuries B.C.E. This hypothesis, however, has also been challenged on the basis of insufficient evidence: The sole palaeopathological finding, porotic hyperostosis, was not considered to be unequivocally diagnostic of thalassemia (Ascenzi & Balistreri, 1977; Ascenzi, 1979).

On the other hand, Angel (1964) proposed that the distinctive osseous pathology manifested by a portion of the skeletal material from the Bronze Age in Greece and
Cyprus was indeed a result of thalassemia. Although his differential diagnosis of the skeletal pathology includes a variety of other diseases (Caffey, 1957), the findings of porosity combined with hyperostosis in a typical bodily distribution led him to believe that the affected bones indicated thalassemia. His thesis gained strength from the fact that thalassemia provides a selective advantage to heterozygotes against the malarial plasmodia, which is thought to have been prevalent in the Mediterranean region at that time.

Angel's subsequent studies (Angel, 1969, 1973, 1975, 1978, 1984), including much older skeletal remains, substantiated his earlier hypothesis. Thus palaeodemographic analysis of the Nea Nikomedeia populations (ca. 5500 B.C.E.) revealed that malaria was the major killer of Neolithic children and a major detriment to adult health. The causative falciparum malarial agent presumably produced a concomitant rapid rise in mutant human hemoglobins such as is seen in thalassemia (Angel, 1984).

The newly established farming peoples in the Eastern Mediterranean region in the Neolithic period were more prone to malaria than were the preceding Palaeolithic hunter-gatherers, probably because the early farms were located on soft marshy soils with "standing" water sources (Angel, 1973) where the Anopheles mosquitoes could breed.

A recent study on prehistoric populations from South Asia (Kennedy, 1984) shows that the contemporaneous occurrences of agriculture, malaria and thalassemia were not limited to the Eastern Mediterranean region. The identification of thalassemia in the skeletal pathology in both regions (the Mediterranean and South Asia), however, has been founded almost solely on one single criterion - porotic hyperostosis, a type of bony pathology which may not be an exclusive finding in thalassemia (Ascenzi & Balistreri, 1977; Ascenzi, 1979). Indeed, increase in porotic hyperostosis reflects an increase in some form of anemia, but anemia can result from any of several causes, alone or in combination, including dietary habits, parasitism and response to infection, as well as to a variety of genetic factors (Mosely, 1963; Hengen, 1971; Carlson et al., 1974; El Najjar et al., 1976; Cook, 1984). It would appear that skeletal remains showing porotic hyperostosis alone are unable to provide a secure diagnosis of thalassemia and hence a solution to questions relating to the origins and spread of thalassemia in the ancient world. We feel this communication to be of importance not only because we have found what we believe to be the earliest known case of thalassemia, but also because our diagnosis of the disease is based on evidence more substantial than presence of porotic hyperostosis alone.

Material and Methods

It has recently been our privilege to participate in the discovery and excavation of the largest and best preserved prehistoric settlement found on the sea floor and the only one to contain human skeletal remains in situ (Hershkovitz & Galili, 1990). The site is Atilt-Yam in Israel, probably an ancient fishing village, located 10 km. south of Haifa Bay and 300 meters off the coast. It is dated culturally and radiometrically to the latest phase of the Pre-Pottery Neolithic B period (ca. 6000 B.C.E.). To date, twenty-six human skeletons in various stages of preservation have been found (Hershkovitz et al., 1989).

Thalassemia-like changes similar to those documented by Angel in the Neolithic Nea Nikomedeia populations from Greece, were seen in the lumbar and thoracic vertebrae in two cases, and in enlarged and thickened crania in two other cases. But the most suggestive evidence for thalassemia came from one skeleton (Homo 25), a young male 16-