Toxins and Breast Cancer


Prion Diseases

David A. Harris, MD, PhD
From the Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri, USA

THE DISEASES

Prion diseases, sometimes called spongiform encephalopathies, are fatal neurodegenerative disorders that have attracted enormous attention, both for their unique biological features and for the threats they pose to public health. This group includes four diseases of human beings (Creutzfeldt–Jakob disease [CJD], kuru, Gerstmann–Sträussler syndrome, and familial familial insomnia) and several diseases of animals, the most well known being scrapie in sheep and goats and bovine spongiform encephalopathy (BSE, or “mad cow disease”) in cattle. The primary symptoms of prion diseases include dementia, ataxia, and myoclonus. Characteristic neuropathologic features include cerebral amyloid plaques and spongiform degeneration of the brain. Prion diseases are quite rare, with an estimated overall prevalence of one to two per million. They share certain features with Alzheimer’s disease, a much more common neurodegeneration disorder, including the presence of dementia and cerebral amyloidosis. Unlike Alzheimer’s disease, however, prion diseases are infectious.

Three manifestations of prion diseases are recognized. The infectious manifestation is most dramatically exemplified by kuru, a neurodegenerative disease that was first described by Carleton Gajdusek in an aboriginal tribe in New Guinea and that was found to be transmitted by ritual cannibalism. BSE is another example of the infectious etiology of prion diseases. This prion disorder of cattle reached epidemic proportions in the United Kingdom in the early 1990s, with as many as 200,000 animals being affected. BSE arose because of the practice of rendering sheep and cattle parts into feed for livestock. It is presumed that a change in the temperature used for the rendering process allowed infectious prion particles to escape inactivation and to be spread throughout the cattle population from contaminated feed. The BSE epidemic has had serious implications for human health because of the emergence in 1996 of a variant form of CJD that has now affected approximately 50 patients in the United Kingdom and 1 in France. These patients are much younger (30 years old, on average) than those with conventional CJD, and the pathology and other features of their illness are also unique. There is now substantial evidence, based on both biochemical and transmission data, that this variant form of CJD was acquired by ingestion of beef contaminated with BSE. Because of the long incubation period for prion diseases (up to 40 years), it is still too early to tell whether variant CJD will turn into a major epidemic. Other examples of inadvertent spread of prion diseases include cases of CJD that resulted from contaminated dura-mater grafts, corneal transplants, neurosurgical instruments, and cadaveric growth hormone. There is also debate about whether infection can occur through blood transfusion or administration of blood-derived products.

There are also genetically determined forms of prion diseases. About 10% of the cases of CJD and all cases of Gerstmann–Sträussler syndrome and familial familial insomnia are inherited in an autosomal-dominant fashion. These cases are all attributable to germline mutations in the gene encoding the prion protein (PrP) on...
chromosome 20. Point mutations occur in the C-terminal half of the PrP molecule and are associated with CJD, Gerstmann–Sträussler syndrome, or fatal familial insomnia. Insertional mutations, which are associated with CJD, occur in the N-terminal half of the protein and consist of one to nine additional copies of an octapeptide repeat that is normally present in five copies. Familial prion diseases have been modeled in both cultured cells and transgenic mice.10,11 A third manifestation of prion diseases is the sporadic forms, which have no obvious genetic or infectious etiology. Most cases of CJD are considered to be sporadic in nature. Interestingly, brain material from individuals afflicted with either inherited or sporadic form of prion disease is infectious and will usually induce disease when inoculated into laboratory animals.9 Prion diseases are unique in being both inherited and infectious.

THE INFECTIOUS AGENT

A great deal of the scientific interest in prion diseases has centered on the chemical nature of the infectious agent. Early experiments demonstrated that the infectious agent was relatively insensitive to treatments that inactivate DNA and RNA, such as ultraviolet irradiation, whereas protein denaturants abolished infectivity.12 These results led Stanley Prusiner to propose that the infectious agent was a unique entity, distinct from a conventional virus, which he called a prion (for proteinaceous infectious particle).13 Purification of the infectious agent from the brains of scrapie-infected rodents was undertaken by using an animal bioassay to track infectivity.14 This eventually led to the isolation of highly infectious particles that contained a single type of protein molecule, denoted PrPSc. Amazingly, these preparations appeared to contain little if any DNA or RNA. Building on earlier theoretical speculations,15 Prusiner proposed that the PrPSc protein is infectious in the absence of nucleic acid.

With the advent of cloning techniques, it became clear that PrP is actually encoded by an endogenous gene on chromosome 20, and that it exits in two isoforms.16 PrPSc is the putatively infectious isoform that is seen only in the disease state. PrPC is a normal isoform of the protein that is expressed primarily in the central nervous system and subserves a function that may be related to the trafficking of copper ions.17 The most important observation to emerge in the prion field in recent years is the recognition that PrPC and PrPSc have the same amino-acid sequence but differ dramatically in their conformations. Thus, all forms of prion disease are hypothesized to result from a conformational conversion of PrPC into PrPSc.18 In the infectious etiology, this conversion is thought to be triggered by a physical interaction between host-encoded PrPC and exogenous PrPSc template, which results in the PrPSc conformation being imposed on PrPC. In inherited prion diseases, a pathogenic mutation is presumed to favor spontaneous conversion of PrPC to the PrPSc state, without the necessity for contact with exogenous infectious agent. Sporadic forms may be due to a rare spontaneous conversion of wild-type PrP or to the presence of somatic mutations in PrP. Of course, given the importance of conformational changes in PrP, a great deal of work has focused on determining the structures of PrPSc and PrPSc. It is clear that PrPSc has a much higher content of β-helix than PrPC.19 A three-helix structure for PrPSc has been determined by nuclear magnetic resonance,20,21 but it has not yet been possible to obtain a complete structure of PrPSc.

There is now considerable support for the prion hypothesis. One of the most compelling lines of evidence derives from studies of PrP transgenic and knockout mice. In a particularly important experiment, it was demonstrated that PrP-null mice are completely resistant to prion infection.22 This demonstrates conclusively that endogenous PrP substrate is essential for propagation of infectivity and development of pathology. In another experiment, it was shown that introduction of a hamster PrP transgene can abolish the species barrier that normally prevents infection of mice with hamster prions.23 This result suggests that prion propagation involves a species-specific physical interaction between exogenous PrPSc and endogenous PrPC. Although it has become increasingly difficult to accommodate this and other evidence with a viral theory of pathogenesis, it must be emphasized that what is arguably the most definitive test of the prion hypothesis has not been successfully performed: the generation of infectious agent in the test tube by experimental manipulation of either recombinant or synthetic PrP.24,25 This does not in any way invalidate the prion theory, but it is likely to reflect the difficulty of reconstituting in vitro a structural transformation in PrP that may require several cellular cofactors.26

THE GENERALITY OF THE PRION CONCEPT

An extremely important development in the prion field during the past several years has been the recognition that prions can be found in non-mammalian species. There is now compelling genetic and biochemical evidence that two proteins of the yeast Saccharomyces cerevisiae (Sup35p and Ure2p) can exist in alternate conformation states that are analogous to PrPsc and PrPSc.27 These conformation states can be transmitted to daughter cells through cytoplasmic mixing, and they alter the functional properties of the respective proteins. Thus, the prion phenomenon is not restricted to a group of rare neurodegenerative diseases in mammals. In fact, it seems likely that an increasing number of biologic processes in a variety of organisms may be explicable on the basis of transmissible changes in protein conformation.

CONCLUSIONS

Our understanding of prion diseases has advanced dramatically over the past half century. It is now clear that these diseases, once thought to be medical and veterinary curiosities, exemplify novel principles of protein structure and biologic information transfer. Some of these principles may have applicability to other neurodegenerative disorders that involve accumulation of conformationally altered proteins such as Alzheimer’s, Parkinson’s, and Huntington’s diseases. In addition to their intrinsic scientific and medical significance, prion diseases have also assumed tremendous public-health importance. The emergence of BSE and variant CJD emphasizes the need for designing more sensitive procedures for detection of prions in foodstuffs, blood products, and donor organs. Current techniques for assaying PrPSc rely on Western blotting, which is relatively insensitive, or on infectivity assays in rodents, which can take a year or more to complete. Further understanding of the structural nature of the PrPsc-to-PrPSc conversion will undoubtedly allow the design of more sensitive and direct assay methods. Prion diseases currently affect a relatively small number of individuals, but it is sensible to take scientifically justified steps to prevent any potential increase in their incidence.

REFERENCES

Malnutrition: Causes, Consequences, and Solutions

Sarath Gopalan, MD
From the Pushpawati Singhania Research Institute, New Delhi, India

INTRODUCTION

As we enter the 21st century and the new millennium, malnutrition, acting either directly or indirectly, remains the single most important factor impairing health and productivity of large human populations. The ongoing demographic and developmental transition has brought about a steady change in the profile of malnutrition, especially in the latter half of the previous century. This has been particularly noticeable in the developing countries.1 Until approximately 50 y ago, malnutrition was largely considered to be the problem of the poor. Famines, due to acute shortage of food, periodically devastated vast populations in Asia and Africa. Florid, classic nutritional deficiency diseases such as kwashiorkor, kertomalacia, pellagra, beriberi, and goitre took a heavy toll. Thanks to the timely advent of the “green revolution,” gloomy Malthusian prophecies of near extinction of populations from famine were belied. Florid nutritional deficieny diseases were largely brought under control. However, considerable undernutrition reflected in “mild” and “moderate” malnutrition, stunting in children, and anemias in pregnancy associated with low–birth-weight deliveries are still widely prevalent in many parts of the Third World. Thus, nearly half of children younger than 5 y in South Asia are presently stunted and nearly one-third of infants born are of low birth weight (<2.5 kg).2

Although undernutrition continues to be a problem of the poor, especially among children and women of developing countries, there has been disturbing evidence of escalation of the incidence of nutrition-related chronic diseases such as obesity, coronary heart disease, and diabetes mellitus among adults of the relatively affluent sections of the developed and developing countries. As a result, developing countries in particular face the double burden of undernutrition among poor women and children at one end of the socioeconomic spectrum and of malnutrition among the relatively affluent adults of the middle class at the other end.3

There is growing evidence that populations of the Third World, emerging from poverty into affluence with consequent changes in diets and lifestyles, may be more vulnerable and prone to such chronic degenerative diseases. Indian immigrants to the United Kingdom, for instance, have been found to suffer more from coronary heart disease and diabetes than either natives of the United Kingdom or their own national counterparts belonging to their erstwhile socioeconomic class in India.4 The fascinating work of Barker et al.5 suggests that the manifestations of malnutrition at the two ends of the socioeconomic spectrum may indeed be causally and metabolically related. Their observations indicate that intrauterine growth retardation could so “program” the fetal tissues as to render them more vulnerable to nutrition-related disorders such as syndrome X and chronic degenerative diseases in later adult life. In short, according to their far-reaching hypothesis, nutrition-related chronic diseases of adulthood could be the “late” effects of early fetal undernutrition. Those born in poverty with intrauterine growth retardation and attaining affluence in later adult life may be special victims!

CAUSES OF MALNUTRITION

Undernutrition, widely prevalent, especially in developing countries, is part of the so-called poverty syndrome, which has the mutually synergistic attributes of low family income, large family size, poor education, poor environment and housing, poor access to

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Correspondence to: Sarath Gopalan, MD, Consultant in Paediatric Gastroenterology and Clinical Nutrition, Pushpawati Singhania Research Institute, Honorary Director CRNSS, Nutrition Foundation of India Building, C-13 Qutab Institutional Area, New Delhi 110016, India. E-mail: mfl@ren02.nic.in or crnss@hotmail.com