Schindler Disease: an Inherited Neuroaxonal Dystrophy due to $\alpha$-N-Acetylgalactosaminidase Deficiency

R. J. Desnick and A. M. Wang
Division of Medical and Molecular Genetics, Mount Sinai School of Medicine, New York, NY 10029, USA

Summary: The clinical, pathological and biochemical features of a neuroaxonal dystrophy resulting from the deficient activity of lysosomal $\alpha$-N-acetylgalactosaminidase are described. This neurodegenerative disorder was recognized in two brothers who had the typical clinical manifestations and neuropathological lesions observed in patients with Seitelberger disease, the infantile form of neuroaxonal dystrophy. Axonal 'spheroids' were observed histologically in the grey matter, and ultrastructural examination revealed the characteristic formations in dystrophic axons in the myenteric plexus and neocortex. Using a newly synthesized fluorogenic substrate, 4-methylumbelliferyl-$\alpha$-N-acetylgalactosaminide, the markedly deficient activity of $\alpha$-N-acetylgalactosaminidase was demonstrated in the affected brothers while their consanguineous parents had intermediate activities, consistent with the autosomal recessive transmission of this disease. No detectable $\alpha$-N-acetylgalactosaminidase was seen in immunoblots using monospecific rabbit antihuman $\alpha$-N-acetylgalactosaminidase antibodies. Abnormally increased amounts of urinary glycopeptides were observed by high resolution thin layer chromatography. Analytical studies identified four of the accumulating urinary compounds, the blood group A trisaccharide GalNAc$\alpha$1→3(Fuc$\alpha$1→2)Gal and three O-linked glycopeptides, GalNAc$\alpha$1→O-serine and -threonine, NeuNAc$\alpha$2→3Gal$\beta$1→3(NeuNAc$\alpha$2→6)GalNAc$\alpha$1→O-serine and -threonine, and NeuNAc$\alpha$2→3Gal$\beta$1→4GlcNAc$\beta$1→6(NeuNAc$\alpha$2→3Gal$\beta$1→3)GalNAc$\alpha$1→O-serine and -threonine. Of eight unrelated patients diagnosed as having infantile neuraxonal dystrophy by pathological studies, none had deficient $\alpha$-N-acetylgalactosaminidase activity, emphasizing the biochemical heterogeneity underlying this diagnostic entity. These findings document the first delineation of a metabolic defect in an inherited neuroaxonal dystrophy and suggest that the axonal pathology in this disorder, and perhaps in the other neuroaxonal dystrophies, results from abnormal glycoprotein metabolism involving O-linked glycopeptides.
PURSUIT AND PERSISTENCE, A MEDICAL PARADIGM

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rare forms of disease (Harvey, 1657).

The concept of metabolism in blocks is giving place to that of metabolism in compartments. The view is daily gaining ground that each successive step in the building up and breaking down, not merely of proteins, carbohydrates, and fats in general, but even of individual fractions of proteins and of individual sugars is the work of special enzymes set apart for each particular purpose (Garrod, 1908).

The recent identification and rapid delineation of Schindler disease, an infantile neuroaxonal dystrophy due to α-N-acetylgalactosaminidase deficiency (van Diggelen et al., 1987, 1988; Schindler et al., 1989), illustrates two current themes in medicine: (1) That suspicion and/or supposition concerning a possible new disease entity, diagnostic method or treatment modality should be pursued, and that persistence in this pursuit is required for success, and (2) that the application of modern biochemical, somatic cell and molecular biological techniques can facilitate the rapid delineation of the cellular and/or molecular defects in newly discovered disease entities.

William Harvey and Sir Archibald E. Garrod both understood the concept of pursuit and persistence and their accomplishments were seminal in the history of medicine. Both men were practising physicians and experimentalists and both appreciated the importance of investigating ‘rarer forms of disease’ to gain understanding of ‘nature’s ways’. For over a decade, Harvey sought to prove that blood circulated continuously within a closed system. His persistence, against a large and influential opposition based in the tradition of Galenic physiology (i.e., blood was produced in the liver and flowed to the periphery), led to one of the most significant of the early advances in physiology and medicine. Garrod sought to understand the nature of the ‘biochemical individuality’ that caused the specific metabolic defects in the disorders he designated as ‘inborn errors of metabolism’. Today, the spirit of pursuit and persistence continues. However, modern medical science has become so sophisticated that an innovative thought or reasoned suspicion requires not only a stubborn commitment to pursuit, but also a team of resourceful and persistent investigators to bring a given hypothesis to fruition.

Physicians and scientists strive to identify and delineate new disease entities. The application of modern ultrastructural, biochemical and cell culture techniques has facilitated the identification of a variety of new inherited metabolic disorders and disease variants. Of the recently described lysosomal disorders, galactosialidosis (Wenger et al., 1978), Salla disease (Aula et al., 1979), and β-mannosidosis (Cooper et al., 1986; Wenger et al., 1986), it is notable that each had prominent visceral manifestations similar to those found in other lysosomal storage diseases which led to their elucidation (e.g., dysostosis multiplex, cherry-red maculae and/or organomegaly). The key to the recognition of these disorders was physician suspicion, phenotypic clues and the diligent pursuit of the pathological and biochemical defects. Such was the brief historical trail that led Dr Detlev Schindler, a human geneticist