From eponyms to mechanisms: A century of NBIA research

While their deeds in the Nazi era must be damned, Julius Hallervorden (1882-1965) and Hugo Spatz (1888–1969) cannot be separated from the history of research into neurodegeneration with brain iron accumulation (NBIA) as their careers teach relevant lessons, in both science and its ethics. The two had met at the "German Research Institute of Psychiatry" in Munich, founded by Emil Kraepelin (1856-1926), holder of the psychiatry chair. He aimed at working out “natural disease entities” among the manifold affections of mind and brain with the help of disease signatures that were to be identified through studies e.g. of individual disease courses, of heredity, of body fluids or brain tissue.

Spatz, in Munich since 1909, had recently concentrated on iron stains of the brain while Hallervorden with a background in asylum psychiatry had acquired neuropathology skills on his own. Active in Landsberg an der Warthe (now Gorzów Wielkopolski, Poland) as of 1913, he also took the district physician exam - thus enabled to conduct post mortem studies. While in Munich, the self-taught neuropathologist intensively studied one case from his collection. “Martha S.” had died in 1919 and Hallervorden had also secured tissue of her sister “Alma” who had died in Landsberg in 1914. Martha´s brain most conspicuously showed “dark rust-brown discoloration” of globus pallidus and substantia nigra pars reticulata. Microscopic analysis was likely done in Munich and Hallervorden and his mentor published their observations in 1922. Two years later, he published the sister´s case on his own. “Hallervorden´s disease” qualified for handbook entry in 1936 as more cases were recognized with shared clinical features, course, heredity, and neuropathology. For years, however, this novel entity remained among those rare diseases to be diagnosed with certainty only post mortem.

Hallervorden was able to fully concentrate on neuropathology as of 1929 and became a professor at the brain research institute in Berlin-Buch under the direction of Spatz in 1938. In the “Third Reich”, he joined the Nazi party and embraced its eugenic ideas. He lectured in the courses of 1934 and 1935 that were to implement the “Law for the Prevention of Offspring with Hereditary Diseases” of 1933 in practice. Its sterilization campaign was a prelude to the systematic killing, in particular during the 1940/41“Aktion T4”, of thousands of psychiatric patients. Their brains were sent for scientific analysis, including to Berlin-Buch. Hallervorden was a witness of victim gassings in 1940 and he personally removed at least one victim´s brain. Although his Nazi complicity within the “Doctors of Infamy” was known, Hallervorden evaded the Nuremberg Doctors' Trial of 1946/47 and resumed his position at the research institute that had relocated to West Germany, again with

Spatz. Hallervorden died as a highly respected scientist and his role in the Nazi atrocities was seriously brought into focus only in the 1980s. Further use of the Hallervorden-Spatz eponym has since been discouraged, e.g. by calling the condition “Martha-Alma disease”. In the meantime, Seitelberger had published findings in infants with a post mortem phenotype of „ neuroaxonal dystrophy” that was not easy to distinguish from what Hallervorden and Spatz had described. Naming the two conditions NBIA1 and NBIA2, respectively, offered a reasonable solution for the eponym discussion.

The demonstration of iron deposits on magnetic resonance imaging (MRI) completely changed the field´s situation. MRI signal changes compatible with iron accumulation were first published in 1985 and in particular the "eye-of the-tiger sign" profoundly affected clinical practice as NBIA could now be diagnosed in the living. A patient organization, the NBIA Disorders Association, was subsequently founded and, initiated by Susan Hayflick, a workshop was held in conjunction with the first family meeting at the National Institutes of Health in 2000 to advance both research and clinical practice.

The discovery of mutations in the pantothenate kinase gene in 2001 led to further refinement of the naming issue. Causally involved genes now form an essential building block in the naming of the diverse NBIA conditions that are recognized. Over the years, “PKAN” (pantothenate kinase-gene associated neurodegeneration, formerly NBIA1) was joined by other molecularly defined entities such as “PLAN” (formerly NBIA2), “MPAN”, “CoPAN”, and “BPAN”.

The latter, ß-propeller protein-associated neurodegeneration, appears of particular interest. The protein affected (other names: WIPI4 and WDR45) is part of a bulk lipid transfer mechanism that plays an essential role also in VPS13 and XK diseases. It appears as if a circle comes to a close: VPS13A and XK disease, formerly known as chorea-acanthocytosis and McLeod syndrome, share a peculiar feature with NBIA cases. In both, acanthocytes, spiky red cells, are found in the blood and had led to an umbrella term of neuroacanthocytosis (NA). Between 2010 and 2014, the respective patient and scientist groups even held three joint NA/NBIA symposia. Whether the occurrence of acanthocytes in NBIA is restricted to PKAN and what they might reflect as to shared disease mechanisms is as yet unsolved. Research questions like these may benefit from the study of locally increased case numbers such as found in the region of Cabral, Dominican Republic, where a large PKAN cohort is affected by the same mutation.

Turning back to Martha and Alma and other patients described in the past, another question arises. Their diagnoses might have appeared plausible from neuropathology and characteristic iron

findings, but the recently uncovered genetic diversity of NBIA makes one wonder whether their molecular diagnoses truly match. This is for example of interest with respect to reports of Lewy bodies in NBIA. Only in the PLAN and MPAN diseases this now appears certain. Analysis of ancient DNA is easy today, but in contrast to Hallervorden and Spatz we must not sacrifice ethical principles to scientific zeal and for retrospective genetic diagnosis we are bound to use material only of unsuspicious provenance.