Not just neurological stamp collecting – when rare diagnoses lead to fundamental advances

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A clinicopathological-conference (CPC) perhaps exemplifies both what non-neurologists consider neurology to be, and what many neurologists consider to be the pinnacle of their art. A brave discussant is confronted by an invariably obscure and more often than not untreatable case which they are tasked with dissecting in full sight of their peers, armed only with his/her clinical acumen. While ostensibly the aim is to predict the correct diagnosis, equally if not more important is to take the audience on an entertaining journey, explaining the diagnostic thought processes en route. In the CPC reported in this edition of Practical Neurology, Rhys Davies admirably rises to this challenge, elegantly taking us through his reasoning, discarding a few red herrings along the way, before finally and correctly predicting the underlying diagnosis of Nasu-Hakola disease, a very rare genetic form of dementia associated with bone cysts [1].

Cases presented in CPCs are of course poles apart from those encountered in routine neurological practice which is, quite rightly, increasingly concerned with the management of a large range of much more common conditions. A busy general neurologist inundated with patients and targets, and grappling with protocols, digital health records and dwindling administrative support, might be forgiven for finding such rarities an interesting diversion, but of little or no relevance to their practice.

At first glance Nasu-Hakola might well be dismissed as just such an obscure rarity – one exclusively for the neurological philatelists. However, it turns out to be an exemplar for how careful clinical phenotyping and understanding of rare disorders can have a much wider impact. Bi-allelic (homozygous or compound heterozygous) mutations in DAP12, as in the reported case, but also an associated gene, TREM2, cause Nasu-Hakola disease. Different single heterozygous rare variants in TREM2 mutations were subsequently identified as rare but very important risk factors for Alzheimer's disease (AD), first reported in two papers published in the same edition of the New England Journal of Medicine in 2013 [2,3]. The rare R47H TREM2 variant is now know to be carried by around 2% of European ancestry AD patients, with an odds ratio for the risk of developing AD estimated as between 3 and 5 in multiple studies. These observations have evidently had a major impact: a Pubmed search for "TREM2 and Alzheimer's disease" returns 766 results since these initial papers. The increasing knowledge of the pathophysiology of Nasu-Hakola has provided fertile ground for further fundamental research, firmly placing immune and inflammatory pathways on the

causal pathway to Alzheimer's disease [reviewed in 4], and leading to the development of new biomarkers [5,6] and novel potential therapeutic targets

This is, of course, only one of numerous examples of how rare, often genetically inherited, conditions can provide mechanistic insights into more common, sporadic diseases. Within the field of neurodegeneration major breakthroughs have come from the identification of autosomal dominant disorders, e.g. the amyloid cascade hypothesis of AD brought about by the identification of APP mutations causing familial disease [7] and the major impact that followed the discovery that C9orf72 expansions can cause both frontotemporal dementia and motor neuron disease [8]. And akin to the link between Nasu-Hakola and sporadic AD, important advances have come from autosomal recessive conditions including, amongst others, the identification that rare biallelic glucosylceramidase beta (GBA1) gene mutations cause Gaucher's disease, while heterozygous states confer risk for Parkinson's disease (reviewed in [9]).

Such advances are absolutely dependent on careful clinical phenotyping – which in turn is dependent on the finer arts of the neurological method the CPC exemplifies, and on clinical academics able to make links between conditions and to explore common mechanisms. It also underpins the importance of "blue skies" research and research in rare conditions. Just as one would not have predicted that seemingly recherché research into prime number theory would now underpin the encryption used for every transaction we undertake online [10], or that work done on retroviruses causing rare forms of cancers would have such relevance when HIV emerged [11], so one could not predict that research into an extremely rare dementia might one day provide novel therapeutic options for Alzheimer's disease.

In an increasingly pressurised and demanding clinical environment and faced by ever more compressed training programmes, we must ensure that the neurological method is not lost, that we provide opportunities and reduce the barriers for trainees to pursue careers as clinical academics [12], and that we continue to undertake research into rare conditions. Long live the CPC.

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