SILVER SYNDROME

When early in his career **John Russell Silver** described a previously unrecognised familial disease he expected it to remain a minor footnote in the medical record. But some 40 years later, identification of the gene responsible has led to research that is advancing our understanding of a wide spectrum of neurological diseases

It is impossible to predict which of the thousands of papers published each year will be important and which will be consigned to the dustbin of obscurity. Only time will show their proper role, but the exact way in which a disease was recognised is easily forgotten.

In 1959, at the beginning of my career I was working as a registrar in neurology at the Middlesex Hospital, when a young girl presented with a wasted hand and spastic lower limbs. She denied that any other members of her family were affected. I thought that she had an intrinsic tumour of the spinal cord and she was admitted for investigation, but a myelogram found no abnormality.

She subsequently developed a sterile meningitis and became very ill, and her mother came to visit her in hospital. The house officer shrewdly observed that the mother had a similar spastic gait to that of her daughter. The mother was examined and on questioning, it turned out that other members of the family were affected.

Her great aunt had been admitted in 1912 to the National Hospital for Nervous Diseases with a similar condition. She was thought to have either a myopathy or progressive muscular atrophy and was discharged after three months of study. The diagnosis was not established.

Her aunt had been investigated at the London Hospital in 1954 after difficulty in walking and weakness in the hands when she was 19. She was found to have wasting of the abductor pollicis brevis and opponens on both sides, with some weakness of the interossei. She had bilateral carpal tunnel syndrome diagnosed, with the pyramidal signs being attributed to a congenital lesion of the pyramidal tracts.

My attention was drawn to another family when a man was admitted for a cataract operation and was observed to have severe bilateral wasting of the small muscles of his hands and spastic lower limbs. This had been present since the age of 16 but did not prevent his serving in the first world war. Other

members of the family were known to be similarly affected.

Genetic links

Clearly, this was a genetic disorder. I constructed pedigrees and sought help from the department of genetics and eugenics at University College Hospital. Professor Penrose, who was head of the department at the time, was extremely helpful in working out the appropriate investigations and the genetic basis of the disease. He introduced me to Julia Bell and Arnold Carmichael, who had carried out a comprehensive investigation into these familial diseases in 1934.

At that stage Professor Carmichael was the director of the neurological research unit of the MRC at Queen Square. He examined some of the patients and confirmed that he had never seen any condition like it. He suggested I should speak to Julia Bell. She was still working aged over 80 at the Galton Laboratory and painstakingly reviewed her magnum opus,¹ a two volume portfolio of all the families that Carmichael had examined in 1934. She confirmed that my two families did not exist in their records and this was a new disease that they had not seen before.

I visited one of the families in a small village in Bedfordshire and examined 35 relatives. I attempted to carry out linkage studies and determine chromosome pattern but at that stage, these investigations were very limited. I published two papers describing my findings on familial spastic paraplegia with amyotrophy of the hands in 1966.^{2,3}

Fig 1 | Pedigree of the K family
Fig 2 | Wasting of the dorsal interosseous muscles of the right hand of V-3 in the K family

Fig 3 | Wasting of the thenar muscles of the right hand of V-3 in the K family

Fig 4 | Pedigree of the A family

Fig 5 | Wasting of the thenar muscles of II-3 in the A family

Fig 6 | Gross wasting of the thenar muscles and the whole palm of the hand of III-2 in the A family

New leads

Although my description was acknowledged in the literature,^{4,6} it remained an interesting but rather irrelevant footnote until some five years ago when a group of geneticists and neurologists at St George's and the Royal Free Hospital contacted me to say that they had another family with a similar condition. They wished to contact my original families and carry out genetic chromosome mapping studies. Fortunately, I had retained my original notes, which were still legible.

They visited the original family and saw many surviving relatives who I had seen 40 years ago. They confirmed my findings and noted the natural course of the disorder. They have found the chromosome and the gene and identified linkages with other neurological diseases, even links with Alzheimer's disease.⁷⁻⁹ This disease has now been eponymously named Silver syndrome, and far from being a minor footnote in the hereditary group of familial spastic paraplegias, it is beginning to provide the key to unravel how these lethal genes can cause

profound neurological disease.

Just as in Friedreich's ataxia,¹⁰ the mutated gene alters the mitochondria and causes an accumulation of iron. The gene responsible for Silver syndrome has been shown to have links with other hereditary disorders also affecting the mitochondria. Understanding the exact mechanism whereby the gene is expressed will help to determine further the nature of the disease.

It is remarkable that despite two affected individuals being admitted and investigated at two leading neurological hospitals in London under eminent neurologists, the condition was not diagnosed until my patient developed iatrogenic meningitis. At that time, linkage and DNA studies were in their infancies but the analysis of the two families served as a foundation for this important research.

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