HEREDITY IN ANKYLOSING SPONDYLITIS*†

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(RECEIVED FOR PUBLICATION AUGUST 8, 1957)

In recent years the importance of heredity in ankylosing spondylitis has been more widely accepted. Increasing evidence, which substantiates the theory that a susceptibility to the disease is influenced by a genetic factor, is found in families in which parent and offspring, sib pairs, and both members of monozygotic twins have been involved. Most of the reported cases have been brought together in an excellent review by Hersh, Stecher, Solomon, Wolpaw, and Hauser (1950). One of the most interesting family histories is that recorded by Riecker, Neel, and Test (1950), in which five proven cases of spondylitis were found in two generations, and evidence was obtained that the disease was also

present in members of the two preceding generations.

We have studied a family with eight affected individuals in two generations (Fig. 1). In Generation III, which included nine siblings and a miscarriage, ankylosing spondylitis developed in five: two males and three females. Two of the three females each has an affected child, and a third sister, herself unaffected, also has an affected child.

Generation II, the father (II, 3), who died at the age of 86, has a history strongly suggestive of arthritis with painful swollen knees and feet. He suffered from severe back pain and in his youth had to be rolled out of bed. In his generation he was the only one with a record of rheumatic disease. His father (I, 3) also had a history suggestive of arthritis, with such badly deformed feet that he was unable to wear shoes for most of his life. His mother (I, 2) was clear of any symptoms.

* Presented before the Ninth International Congress on Rheumatic Diseases, Toronto, June, 1957.

† This study was supported in part by a grant from the Canadian Arthritis and Rheumatism Society.

Fig. 1.—Pedigree chart demonstrating simple autosomal dominant inheritance in ankylosing spondylitis.

II, 13, the wife of II, 3, and mother of the five affected siblings, had no form of rheumatism or arthritis and there was no known history of rheumatic disease on her side of the family. She was still living when this investigation was initiated.

Radiological examinations were made of all the living adults of the immediate family, 23 individuals. Some of them are living in areas remote from Toronto and we are indebted to the physicians and hospitals who co-operated in the investigation. Complete physical examinations and erythrocyte sedimentation rate estimations were carried out on those who had abnormal radiographs. No x-ray examination was made of the individuals who married into this family, but careful questioning did not reveal any suspicious symptoms. There were no consanguineous matings. No one in Generation V has been examined since they are all under 14 years of age.

Case Reports

Case 1, male, aged 65 years (III, 3), was the first to be affected in this family. He was healthy and fond of athletics until the age of 18 years when he first developed

joint symptoms. When he was 24 years of age he was confined to bed for 4 years because of his arthritis. Examination revealed undoubted ankylosing spondylitis with extensive spinal involvement. In addition he has had attacks of iritis and has been unable to work since the age of 25 years. He has no children.

Case 2, female, aged 62 years (III, 7), is the most mildly affected of the five siblings. She complained of low back pain at 34 years of age, but has had no peripheral joint swelling, generally feels well, and is not incapacitated. She has had one attack of iritis. The radiological findings confirm a diagnosis of ankylosing spondylitis (Fig. 2). She has four children (IV, 7-10), one of whom (Case 6; IV, 8) is also affected.

Case 3, female, aged 59 years (III, 9), suffered low back pain and swollen ankles at the age of approximately 20 years. Examination revealed a marked kyphosis with gross restriction of cervical movement and fusion of the dorsal and lumbar spine. There have been no attacks of iritis. X-ray examination confirmed a diagnosis of ankylosing spondylitis. She has one son (IV, 11), aged 29, who is unaffected.

Case 4, male, aged 54 years (III, 11), had his first symptoms of spondylitis at about 18 years of age. The

Fig. 2.—Case 2, mild ankylosing spondylitis.

entire spine is involved but the peripheral joints are not affected. He has had three attacks of iritis. The diagnosis of spondylitis was confirmed by x ray. He has one son (IV, 15), aged 25, whose x rays are clear.

Case 5, female, aged 51 years (III, 13), first noted pain in the sacro-iliac region when she was 31 years old. The dorsal and lumbar spine are involved and movement of the cervical spine is markedly limited. A left hip arthroplasty was performed in 1952. She has had three attacks of iritis. Her only offspring is IV, 17 (Case 8).

It is of interest to note that the three affected sisters (Cases 2, 3, and 5) were married to three brothers, all of whom are now deceased. There is no history of rheumatoid disease on the husbands' side of the family. The one unaffected brother in this generation (III, 5) died at 60 years of age after a coronary thrombosis. He was not examined and no x-ray films were taken, but he had been in excellent health with no rheumatic complaints. His three children (IV, 2, 3, 6), whose ages range from 27 to 43 years, have all been examined and found to be normal. Three deaths among his grandchildren (V, 3, 4, 7) were the result of Rh incompatibility.

Case 6, female, aged 37 years (IV, 8), the daughter of III, 7 (Case 2), gave a history of pain, which she thought was sciatica, in her early twenties. Spondylitis was not considered as the cause of this pain until this family study was begun. Radiological examination of the sacro-iliac region confirmed the suspected diagnosis of ankylosing spondylitis (Fig. 3).

Case 7, female, aged 28 years (IV, 14), daughter of III, 10, had had no clinical symptoms suggestive of spondylitis, but x-ray films taken in the course of our study showed involvement of the right sacro-iliac joint (Fig. 4, opposite). Because radiological examination revealed no abnormality in her mother (III, 10) or in her two older brothers (IV, 12, 13), these positive findings were unexpected. To eliminate the possibility that the disease might be traced to her father's side, he was contacted for further study. He refused to submit to a physical examination but there was no evidence in his history to suggest that he or his kindred might be affected.

Case 8, male, aged 26 years (IV, 17), is the son of III, 13 (Case 5). As a child he had deformed feet and had to be fitted with special shoes. He began to complain of backache at 20 years of age, but this was attributed to back strain. However, the pain persisted and his

Fig. 3.—Case 6, ankylosing spondylitis in which pain was formerly attributed to sciatica.

Fig. 4.—Case 7, asymptomatic ankylosing spondylitis discovered in the course of the genetic study.

mother began to suspect that he was suffering from the same condition as herself. Her fears were confirmed by radiological examination (Fig. 5, overleaf).

This remarkable family is an excellent illustration of simple autosomal dominant inheritance with slightly reduced penetrance. In dominant inheritance with full penetrance a trait is passed from parent to child without skipping a generation; half of the offspring of an affected parent should be similarly affected. In the kindred we have investigated, 11, 3 probably had ankylosing spondylitis. He passed the dominant gene on to six of his nine children, five of whom developed the symptoms of the condition, while in the sixth the gene, though present, was not evident clinically. The six carriers of the dominant gene had a total of ten offspring, three of whom were affected. The total number of offspring of dominant carriers is nineteen (9+10). Nine of these have the abnormal gene, that is the

expected 50 per cent. There is a slight deviation in the sex ratio: six females to three males instead of the expected 1 : 1 ratio.

Discussion

Riecker and others (1950) pointed out that, although most cases of ankylosing spondylitis are sporadic, in certain families a genetic factor is evident. They suggest that, in these families, because of a common heritage, there may be an accumulation of several modifying genes, so that all members carrying a specific abnormal gene are affected. In other families, though the same abnormal gene may be present in several members, the whole genetic make-up may suppress its action and only sporadic cases appear. They also noted that in familial cases there is an approximate equality of affected males and females, whereas in sporadic cases the majority are males.

Fig. 5.—Case 8, complaint of backache since the age of 20.

Hersh and others (1950) also called attention to this unusual sex distribution. They found that, in the general population, 70 per cent. of the males and only 10 per cent. of the females, who were believed to be carrying the abnormal gene, actually developed spondylitis; but in familial cases where at least one female was affected, the abnormal gene was more stable and all those suspected of carrying the gene developed the disease regardless of sex, especially when the mother was the affected parent. In our study, however, the history suggestive of spondylitis is on the paternal side of the family.

There remains the possibility that many sporadic cases may not have the same genetic aetiology as familial cases. Some may be caused by different genetic factors. Others may be purely environmental or constitutional in origin, the striking difference in the sex ratio suggesting a susceptibility peculiar to the male. Still other cases may be due to mutations.

The possible aetiology of the various rheumatic diseases is being intensively investigated in many centres at the present time, but little attention has

been paid to genetic factors, which appear to be of considerable importance, particularly in ankylosing spondylitis.

Until a cure is found, the early diagnosis and treatment of these patients is of vital importance. Demonstration of simple dominant inheritance in ankylosing spondylitis is, therefore, of practical significance.

In this family study, one woman (IV, 14; Case 7) was completely asymptomatic and her condition was revealed only in the course of the investigation. This would indicate that greater stress might be placed on the investigation of close relatives of those suffering from ankylosing spondylitis.

Summary

It has been proposed by Hersh and others (1950) that ankylosing spondylitis is inherited as a single autosomal dominant gene with an overall penetrance rate of 70 per cent. for males and 10 per cent. for females. However, in those sibships containing at least one affected female, especially when the affected

parent is the mother, penetrance is increased to almost 100 per cent. in both sexes. A pedigree is here presented which in general supports this theory. Among a total of nine sibs, two males and three females were found to be affected. Radiological examinations of all surviving adults in this family, including fifteen individuals in the following generation, revealed the same condition in a daughter and a son of two of the affected sibs. Detailed histories of the parents of the affected sibs gave evidence strongly suggestive of ankylosing spondylitis in the father, but not in the mother. The pattern of inheritance is that of a dominant gene transmission and the unusual number of affected individuals in a pedigree containing affected females gives support to the hypothesis of increased penetrance in such families. However, the mother is not the affected parent in this pedigree.

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Hérédité dans la spondylarthrite ankylosante

RÉSUMÉ

Hersh et ses collègues (1950) ont énoncé que la spondylarthrite ankylosante est transmise par un seul gène autosomatique dominant, ayant le chiffre total de pénétration de 70 pour cent pour les mâles et de 10 pour cent pour les femelles. Dans une génération, cependant, comportant au moins une femelle affectée, surtout lorsque le parent affecté est la mère, le chiffre de pénétration atteint presque 100 pour cent des deux sexes. On présente ici un arbre généalogique supportant cette

théorie en général. Sur neuf enfants, deux mâles et trois femelles étaient affectés. Un examen radiologique de tous les adultes vivants de la famille, y compris 15 sujets de la génération suivante, révèle la même affection chez une fille et un de ses cousins. Dans les antécédents de leurs parents on trouva une forte indication de spondylarthrite ankylosante chez le père, mais non pas chez la mère. Il s'agit donc ici d'un mode de transmission par un gène dominant, et le nombre extraordinaire de sujets atteints dans un arbre généalogique comportant des femelles atteintes, supporte l'hypothèse d'une pénétration augmentée en telles familles. On note, cependant, que la mère n'est pas le parent affecté dans cet arbre généalogique.

Herencia en la espondilartritis anquilosante

SUMARIO

Hersh y sus colegas (1950) han enunciado que la espondilartritis anquilosante se transmite por un solo geno autosomático dominante, con una cifra total de penetración de un 70 por ciento para los machos y de un 10 por ciento para las hembras. Sin embargo, en una generación que contiene al menos una hembra afecta y particularmente cuando se trata de la madre, la cifra de penetración alcanza hasta el 10 por ciento en ambos sexos. Se presenta aquí un árbol genealógico que, en general, da apoyo a esta teoría. De nueve hijos, dos machos y tres hembras fueron afectas. Un examen radiológico de todos los adultos sobrevivientes de la familia, incluso con 15 sujetos de la generación siguiente, reveló la misma afección en una hija y en uno de sus primos. En los antecedentes de los parientes de éstos hubo una fuerte indicación de espondilartritis anquilosante en el padre, pero no en la madre. Se trata aquí, pues, de un modo de transmisión por un geno dominante, y el número extraordinario de sujetos afectos en el árbol genealógico que contiene hembras afectas, da apoyo a la hipótesis de una penetración aumentada en tales familias. Se nota, sin embargo, que en este árbol genealógico la madre no es el pariente afectado.