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Neurofibromatosis in Monozygotic Twins: *A Case Report*

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A case report is given of a pair of monozygotic twin girls with neurofibromatosis caused by a new mutation. The symptomatology was dominated by a neurofibrosarcoma on the leg of one twin and by a large plexiform neurofibroma on the neck of the other twin. Otherwise, the disease showed similar, although not identical or mirror-image distribution of subcutaneous neurofibromas and café-au-lait spots. The twins had identical HLA and blood group antigens and the same chromosome aberration. These case reports indicate that nonhereditary factors may influence the manifestations of neurofibromatosis. A review of the literature on monozygotic twins with neurofibromatosis is given.

Key words: Neurofibromatosis, v. Recklinghausen disease, Monozygotic twins

INTRODUCTION

Neurofibromatosis is an autosomal, dominantly inherited disease with a high rate of new mutations and a wide range of manifestations, including somatic, neurological, and psychiatric symptoms. Since studies in twins may provide valuable information about the relative importance of such symptoms, we have collected anamnestic information and carried out extensive physical, neurological, and psychiatric investigations of a pair of monozygotic, (MZ) twin girls with neurofibromatosis, and we have compared our findings with results from similar studies.

METHODS

Anamnestic data were analyzed and compared in a pair of MZ twin girls with neurofibromatosis, defined, according to Crowe et al [6], by the presence of at least six café-au-lait spots no less than 1.5 cm in diameter and by neurofibromas verified histologically. To determine whether any first-degree relatives were also affected by the disease, the twins' mother and sister were examined, but the father

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refused physical examination and had to be evaluated from anamnestic data and a personal interview. Objective investigations were made of the somatic, neurological, and psychiatric status of the twins. Psychiatric ratings were performed according to the CPRS [2]. Blood samples were obtained for chromosome analysis with G- and C-banding techniques [1,4] and for serological typing and determination of blood group antigens.

CASE REPORT

No case of neurofibromatosis was recognized among the first-degree relatives. The twins showed indentical HLA antigen (A 2, 3; B 18; W 35; Cw 4; DR 4), blood group antigen (B Rh(+)), and Rh type (CcDEe; Kell (−); Fy(a+b+); Jk(a+b−); P_1(+); Le(a+b−); MM; Ss). The chromosome analysis showed in both twins 22 pairs of autosomes and XX and a deletion in the heterochromatin region of chromosome 16.

During pregnancy the 24-year-old mother of the twins suffered from albuminuria, and at delivery she had secondary insufficiency of contractive activity. Both twins were delivered by forceps.

The twins' father was strict and domineering, but conditions in the home were reported to have been good. The parents divorced when the twins were 10 years old. They attended normal school classes and had almost identical grades, somewhat below average.

Twin 1 reported nervous problems in childhood; she was sensitive and shy and trusted only her twin sister. Between the ages of 7 and 22 years she had seven operations for repeated resections of a large plexiform neurofibroma along the neck and behind the left ear. Several neurofibromas required excision.

Twin 2 reported problems during the school years. She felt an outsider and was teased and bullied. There was some truancy, and also nail-biting and fear of darkness during childhood. At the age of 13 years she underwent surgery with amputation and hemipelvectomy on the right side for neurofibrosarcoma in the leg. For a whole year after the operation she refused to cooperate in training for walking with a prosthesis.

At the time of this study the twins were 24 years old, unmarried, had no children, and were employed as office clerks.

The results of the comparisons between the twins are recorded in Table 1. There was concordance between the twins in most factors investigated. The somatic examinations revealed no major differences, and neither girl had neurological complications of the disease. They had almost the same number of café-au-lait spots, though they were not equal in distribution; both had axillary freckling. The neurofibromas, about 100 in each girl, were in both distributed over the trunk and limbs, but only one of the twins had some (about 10) on the face.

Both twins had experienced mild forms of psychiatric symptoms in childhood but neither had required treatment. As assessed by interview, there were a few slight neurotic symptoms in both twins. Both were estimated to have normal or slightly below normal intelligence levels.

Both twins had complications of their disease at an early age: one had been operated on for a neurofibrosarcoma in the leg and the other had had a plexiform neurofibroma removed from the neck.

DISCUSSION

Comparison of the MZ twins with neurofibromatosis showed remarkable similarity in most respects. In somatic, neurological, and psychiatric findings, as well as in intellectual

level, they were almost identical. The number and distribution of café-au-lait spots and cutaneous neurofibromas were similar, though not identical. A comparison between the results of this and other studies on MZ twins with neurofibromatosis is shown in Table 2. It is, however, difficult to interpret data from previous studies, for in earlier days the indentification of MZ twins was uncertain, due to lack of techniques such as determination of HLA antigen and blood group serology. Furthermore, lack of data concerning first-degree relatives makes it difficult to separate hereditary and spontaneous forms of neurofibromatosis. It is also probable that the symptomatology changes with time and progress

TABLE 1. Anamnestic and Objective Findings Compared in a Pair of Monozygotic Twin Girls

	Twin 1	Twin 2
Zygocity tests		
HLA antigen	Identical	Identical
Blood group antigen	Identical	Identical
Rh type	Identical	Identical
Chromosomes	Identical	Identical
Birth		
Birth order	1	2
Birth weight	2,660 gm	2,620 gm
Type of delivery	Complicated	Complicated
Somatic status		
Height	155 cm	155 cm
Weight	Normal	Slight overweight
Growth of hair	Normal	Normal
Congenetial malformations	None	None
Neurological status	Normal	Normal
Psychiatric symptoms		
Nervous problems in childhood	Mild	Mild
Psychiatric treatment	None	None
Psychopharmaca	Never	Never
Current symptoms	Tension and anxiety	Restlessness and Irritability
CPRS score	5.5	2.0
Intelligence level		
Assessed at interview	Normal	Normal
School grades	Below average	Below average
Café-au-lait spots		
Number	8	6
Localization	Trunk	Trunk
Axillary freckling	Bilateral	Bilateral
Neurofibromas		
Number	100	100
Localization	Trunk, Limbs and chin	Trunk, limbs
Tenderness	Yes	No
Neurofibrosarcoma	No	Yes
Plexiform neurofibroma	Yes	No
Major surgery required		
Age at first operation	7	13
Type of operation	Plastic surgery	Amputation and hemipelvectomy

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TABLE 2. Condordance Between Symptoms of Neurofibromatosis in Studies on Monozygotic Twins

Author	Variables investigated	Concordance (+) or discordance (−) in number, distribution, or degree of symptom
Borberg [3]	Café-au-lait spots	+
	Neurofibromas	+
	Intelligence level	+
Cartwright [5]	Precocious puberty	+
	Malignant glioma	+
Dresner and Montgomery [8]	Opticus glioma	+
Diekman et al [7]	Plexiform neurofibroma	−
Riccardi et al [10]	Café-au-lait spots	−
	Neurofibromas	−
	Epilepsia, hydrocephalus	−
	Scoliosis	−
Vaughn et al [11]	Café-au-lait spots	+
	Neurofibromas	+
	Opticus glioma	−
Present study	Café-au-lait spots	+
	Neurofibromas	+
	Plexiform neurofibroma	−
	Neurofibrosarcoma	−
	Intelligence level	+

of the disease, and therefore age-matching would be required for adequate comparisons between pairs of twins.

It is of particular interest that the twins in this study also showed dissimilar manifestations of neurofibromatosis: a neurofibrosarcoma and a plexiform neurofibroma, respectively. There appear to be no previous reports of a neurofibrosarcoma in one of a pair of MZ twins. As seen in Table 2, opticus glioma was described in two earlier studies on MZ twins, showing concordance in one study and discordance in the other. Plexiform neurofibroma was found in one of MZ twins in a study by Diekman et al [7].

The difference found in our twins indicate that nongenetic factors modify the disease process. It cannot, however, be excluded that these apparently dissimilar manifestations may have a close relationship. The fact that plexiform neurofibroma has a stronger tendency to malignant change than any other neurogenic tumor [9] suggests that the neurofibrosarcoma in the leg of one twin could have developed from a plexiform neurofibroma. The twins might have a hereditary predisposition for developing plexiform neurofibromas, regardless of localization, and the risk of malignancy thus might be increased.

There is a predominance of female MZ twins in the literature—all the cases from Table 2 but Cartwright's twins are females. Whether this observation reflects a true sex difference is difficult to decide at present.

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