

Clinical variability in Sanfilippo B disease: a report on six patients in two related sibships

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Two closely related sibships are described in which six definite and two probable patients with Sanfilippo B disease were found. The wide variation in phenotypic expression in these patients is suggestive of a genetic background effect.

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The Sanfilippo syndrome (MPS-ose III) is an autosomal recessive disorder of mucopolysaccharide metabolism. Large quantities of heparansulfate are excreted in the urine, and this has diagnostic importance. Genetic heterogeneity has been proved by the identification of two distinct enzyme deficiencies: i.e. a deficiency of heparansulfatase in Sanfilippo A (Kresse & Neufeld 1972) and of N-acetyl- α -D-glucosaminidase in Sanfilippo B (O'Brien 1972). Recently, a deficiency of an α -glucosaminidase has been suggested (Kresse & von Figura, cited by Witting et al. 1975).

The Sanfilippo syndrome is characterized by early and severe mental deterioration, coarse facial features, megaloccephaly, and hepatomegaly. Moderate skeletal changes are the rule. However, wide variation in phenotypic expression has been reported.

We report our findings in two related sibships with Sanfilippo B disease, which illustrate the occurrence of wide clinical variability within one family.

Materials and Methods

The family under study lives in a small village in the southern part of The Netherlands. The probands are two sisters and their female first cousin, all of whom are inmates of the same institution for the mentally retarded. Their fathers are brothers, and their mothers are sisters. Pedigree analysis revealed several instances of consanguinity (Fig. 1).

The diagnosis of Sanfilippo B disease was proved in the three probands, and subsequently in three relatives (Liem et al. 1976). Two other probable patients had

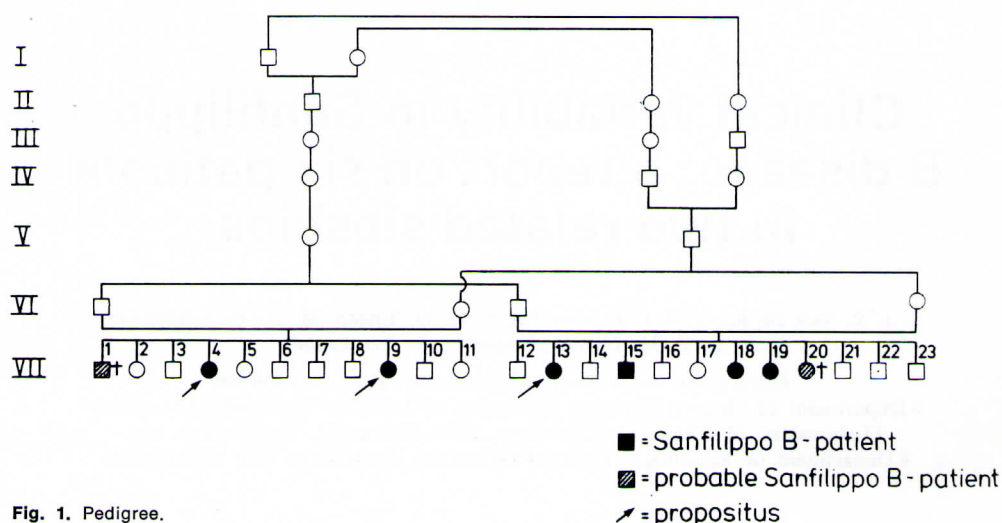


Fig. 1. Pedigree.

already died. All living patients were examined by the authors, and all available data on the patients and the deceased relatives were collected from hospital records and from parents.

Results

The main clinical data are summarized in Tables 1, 2, and 3. Considerable variation

is obvious, although the manifestations were unusually mild in most of the patients. As a rule, speech development was fairly normal, and mastery of language was lost either late or not at all. However, patient VII.20 has never spoken, and in patient VII.9 speech was lost at the age of 6 years. Mental deterioration was of late occurrence, so that most of the patients had attended the first grade of a primary school, and

Table 1

Age (in years) of patients at time of examination or death and at various stages of development

	Definite patients						Probable patients	
Number in pedigree	VII.4	VII.9	VII.13	VII.15	VII.18	VII.19	VII.1	VII.20
Examined/deceased	27	21	26	24	21	18	†21	†15
Started walking	2	1.2	1.4	1	1.4	1.4	0.8	6
Started talking	late	1.5	1.5	1.5	1.5	4	1.5	never
Recognition of mental retardation	6	4	7	6-7	6	6-7	6	from birth
Decline in verblability	not yet	6	21	not yet	not yet	14	ca. 18	-
Decrease in motor ability	not yet	not yet	21	not yet	not yet	not yet	none	never walked well
Institutionalized	24	17	11	no	no	14	+	+

Table 2
Relevant clinical data

	Definite patients						Probable patients	
Number in pedigree	VII.4	VII.9	VII.13	VII.15	VII.18	VII.19	VII.1	VII.20
Sex	F	F	F	M	F	F	M	F
Height (cm)	165	165	160	192	169	158	stated to be normal	148
Head circumference (cm)	54	52.5	53	58.5	57	53	?	stated to be increased (hydrocephalus internus)
Typical facies	+	+	±	-	-	±	±**	±**
Coarse hair	+	±	±	-	±	±	?	?
Speaks or had spoken in sentences	-	+	+	+	±	-	+	-
Hepatosplenomegaly	-	-	-	-	-	-	?	-*
Inguinal hernia	-	-	-	-	-	-	+	-

* = post-mortem examination.

** = judged from photographs.

Table 3
Radiographic findings

	Definite patients						Probable patients	
Number in pedigree	VII.4	VII.9	VII.13	VII.15	VII.18	VII.19	VII.1	VII.20
Wide ventricles	0	0	0	0	0	0	+	±*
Thick calvarium	±	0	±	±	-	-	+	0
Pelvic anomalies	+	+	-	-	0	-	0	0
Broad clavicles	0	+	+	-	0	-	0	0
Spoon-like ribs	0	+	-	-	0	-	0	0

* = post-mortem examination.

0 = no data.

patient VII.15 (Fig. 2), aged 24 years, is still "working" and has social contacts. But patient VII.20 had been retarded from early infancy, and patient VII.13 had to be institutionalized at the age of 11 years as a deep, unmanageable idiot. There were few disturbances of locomotion, even at an older age, but patient VII.20 never walked well. Patient VII.4 (Fig. 3) and patient VII.9 had a typical Sanfilippo facies, while others had not.

Discussion

Over 100 cases of Sanfilippo syndrome have been described in the literature so far. Spranger (1972) gave an excellent description, based on 68 cases reported before 1970; and Rampini (1976) reviewed 77 cases.

In the typical Sanfilippo patient early development is normal; but at the age of 2 to 4 years development stops and mental



Fig. 2. Patient VII.15 at 24 years of age.



Fig. 3. Patient VII.4 at 27 years of age.

degeneration – often rapid – sets in. Speech is often poor and is lost early. Later, the gait becomes unsteady. Muscular atrophy and contractures develop, and the patients become bedridden. Death occurs before or soon after puberty.

Physical examination reveals coarse facies with abundant, bristly hair and a markedly increased head circumference. The liver and, less frequently, the spleen are enlarged, and inguinal and umbilical herniae are not uncommon. Height is normal in the first decade, but below normal in older patients. Frequently-occurring skeletal anomalies include: thickened calvaria, ovoid vertebral bodies, and mild pelvic dysplasia. Dilatation of the ventricular system is often seen.

There is, however, considerable variation in this clinical expression. Some patients are

retarded from early infancy (Abraham et al. 1970), whereas others may attend the first grades of primary school (Gordon & Thursby-Pelham 1969). Some patients are confined to wheelchairs long before reaching their teens (Maroteaux & Lamy 1964), but others remain ambulant (McKusick et al. 1965). Some patients die in a cachectic state long before the age of 10 years (Danks et al. 1972), while others survive quite well into the fourth decade (Giesberts 1976). Wide variation in bone involvement has also been reported (Langer 1964).

Clinical variability is a well-known phenomenon in heritable disorders and can often be attributed to genetic heterogeneity. Most authors presume, however, that in the Sanfilippo syndrome genetic heterogeneity does not produce phenotypic differences (Mc-

Kusick 1972, Beaudet et al. 1975). This was substantiated by Farriaux et al. (1974) who could not demonstrate significant differences between three Sanfilippo A patients and three Sanfilippo B patients. This is in agreement with our observations in 45 cases of type A and 15 cases of type B Sanfilippo disease (van de Kamp, to be published).

However, clinical variability may also derive from differences in genetic background. In contrast to the variation due to genetic heterogeneity, this variability occasionally occurs intrafamilially. The family described here offers an example of intrafamilial variability, since remarkable phenotypic differences were found between the diseased sibs. These findings suggest that in the Sanfilippo syndrome the genetic background can exert a strong influence on the phenotypic expression. Furthermore, the patients in this family are remarkable in that they barely conform to the classical picture of the Sanfilippo syndrome.

Awareness of the possibility of such wide variation might help in the earlier recognition of patients and, in some cases, could perhaps contribute to prevention.

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