Phenotypic variability in siblings with type III spinal muscular atrophy

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SMA in the light of recent findings in mouse models.67

Autosomal recessive spinal muscular atrophy (SMA) shows
substantial phenotypic variability, presenting at a variety of
ages from infancy to adult life. Diagnostic difficulties may
arise because SMA sometimes produces a dystrophic or
myopathic phenotype rather than classical neurogenic
abnormalities. Two brothers are described who illustrate this
principle and highlight the increasing importance of mole-
cular genetics in investigating patients with neuromuscular
diseases. The findings are discussed in the light of recent
observations in a mouse model of SMA.

Spinal muscular atrophy (SMA) is characterised by
progressive degeneration of anterior horn cells. Four
subtypes of the common autosomal recessive form are
recognised, based on age at onset of symptoms and clinical
course.1 Type I SMA (Werdnig–Hoffmann disease) is the
most severe, with weakness developing within the first six
months of life and death within two years. In type II SMA,
weakness usually begins between three and 15 months of
age. These children never manage to stand or walk unassisted
but they survive into adolescence. In type III SMA
(Kugelberg–Welander disease), onset is usually after the
second year of life and progression is variable. The disease is
characterised by proximal weakness, predominantly of the
legs. Patients typically have normal milestones in the first
year of life and manage to stand and walk unaided but have
problems with running and jumping. They usually maintain
ambulation over many years and the prognosis is generally
good. Type IV (adult onset) SMA usually presents with a limb
girdle phenotype in the third decade.2

Autosomal recessive SMA is caused by mutations in the
telomeric copy of the survival motor neurone gene (SMN-1)
at 5q11.1–13.3.3 Deletions of exon 7 and 8, or 7 alone, account
for over 95% of SMA cases.4 Most of the remaining cases have
intragentic point mutations in the SMN-1 gene. The molecular
mechanisms by which SMN-1 mutations cause SMA remain
unknown. Other genes at the SMA locus have been reported
as candidate modifiers for the SMA phenotype, of which
SMN-2 is thought to be the most important.5

Intrafamilial phenotypic variation in SMA is rare. Previous
reports have described differences in severity within the same
family.6 In contrast we report two brothers with identical
homozygous deletions of exons 7 and 8 of SMN-1 but with
strikingly different pathological phenotypes. We highlight the
importance of molecular genetics as part of the routine
investigation of neuromuscular disorders and discuss a
possible molecular basis for the discordant phenotypes of
SMA in the light of recent findings in mouse models.6,7

CASE HISTORIES

Patient 1

A 16 year old boy first became aware of proximal leg
weakness about one year before his referral. He had achieved
normal motor milestones and managed sports at school. He
had noticed some thinning of his thighs and a fine tremor of
his hands and head. He had not suffered muscle pains or
cramps. His parents were first cousins and he had a five year
old brother and four sisters. The brother (patient 2) was also
eventually found to have neuromuscular problems but the
sisters were asymptomatic.

On examination he had mild neck flexion weakness and
normal extension. There was generalised muscle wasting
with severe symmetrical weakness, affecting proximal more
than distal musculature. There was no fasciculation. His
calves were not hypertrophied. Reflexes in the upper limbs
were all reduced and the knee jerks were brisk. He had a fine
tremulousness of his limbs and head, and showed a typical Gowers
manoeuvre. His gait was normal and he could hop on either foot.

Serum creatine kinase (CK) was increased to 1181 U/l
(0–220). Nerve conduction studies were normal. Quantitative
electromyography of the right vastus lateralis showed no
fibrillations or fasciculations, but the motor units were of
short duration and reduced size, suggesting a chronic
myopathic process. Muscle biopsy from the left quadriceps
(fig 1A) showed myopathic changes, with variation in fibre
size, a significant increase in frequency of internal nuclei, and
occasional necrotic fibres. None of the features commonly
associated with neurogenic disorders was observed. HLA
staining was negative except on necrotic fibres and some
occasional small (regenerating) fibres. Dystrophin staining
was normal and DNA analysis showed no deletions in the
dystrophin gene. However, there was homozygous deletion of
exons 7 and 8 of the telomeric copy of the SMN gene,
confirming a diagnosis of SMA.

The patient was encouraged to undertake a weight training
programme combined with a high protein diet. At one year
follow up his muscle strength and function had remained
stable.

Patient 2

This five year old boy was examined at the time of his elder
brother’s evaluation. He had no specific symptoms and his
father did not feel that he was lagging behind his peers in
sports at school. However, he ran in a rather flat footed
fashion, had difficulty hopping, and showed a partial Gowers
manoeuvre. He had some neck weakness and mild proximal
weakness in both upper and lower limbs, with preserved
distal strength. His calves were not hypertrophied. He had
diminished knee jerks and intact ankle jerks. All his blood
results were normal, including CK.

His muscle biopsy (fig 1B) showed frequent atrophic
angular fibres that stained intensely with oxidative enzymes,
but there was no evidence of fibrosis, inflammation, or

Abbreviations: SMA, spinal muscular atrophy; SMN, survival motor
neurone
necrosis. Histochemistry revealed fibre type grouping, indicating denervation with reinnervation, but no grouped fibre atrophy. On genetic analysis there were no deletions in the dystrophin gene, but, like his older brother, he had homozygous deletions of exons 7 and 8 of the telomeric copy of the SMN gene.

At one year follow up he was able to run relatively well but continued to have difficulty rising from the supine position.

**DISCUSSION**

Homozygous deletions or mutations of exon 7 of the SMN1 gene have been found in more than 95% of SMA cases. Both our patients achieved normal milestones in the first year of life but developed symptoms or signs after the age of two years, consistent with type III SMA. However, the diagnosis of type III SMA was not immediately apparent in the proband (patient 1) as his laboratory abnormalities were more in keeping with a muscular dystrophy or myopathy. By contrast, his younger brother (patient 2) had a normal serum CK and histopathological abnormalities consistent with classical SMA.

About a quarter of type III SMA patients are reported to have a dystrophic phenotype with high serum CK levels and "myopathic" histopathology. While there have been previous reports of affected siblings having different degrees of clinical severity, ranging from type I to type III, there have been no reports of siblings with the same SMN-1 mutation having discordant clinical and pathological phenotypes of type III SMA.

The biological factors determining a dystrophic rather than the classical neurogenic phenotype are unknown. In patient 1, there was no suggestion of an immune reaction because there was no upregulation of MHC expression on the non-necrotic fibres. Phenotypic variation in SMA might reflect genetic factors. Three other genes within the SMA locus—namely, neuronal apoptosis inhibitory protein (NAIP), H4F5, and SMN-2—have been reported to modify the SMA phenotype. However, SMN-2 is thought to be most important as the amount of SMN protein expressed in tissues appears to be inversely correlated with clinical severity.

Recently, a conditional transgenic mouse model of SMA has been reported. The investigators showed that if exon 7 of the mouse orthologue of SMN-1, *smn*, is deleted in neurones, affected mice die prematurely and have severe muscle denervation. However, if exon 7 of *smn* is deleted in skeletal muscle, the mice die prematurely and have muscle necrosis and a dystrophic phenotype. Thus the varying phenotypes in our siblings might reflect differential amounts of SMN protein expression in muscle compared with motor neurones, owing to somatic mosaicism of the SMN-1 gene in these tissues.

Secondary myopathic abnormalities are well recognised in cases of primary denervation and reinnervation. It has been suggested that myopathic changes in muscle biopsies of type III SMA are usually seen only in the later stages of disease and it is possible that "neurogenic" abnormalities would have been evident in case 1 if the biopsy had been done earlier. However, he was investigated only a few months after the onset of weakness, suggesting that his "myopathic" phenotype is indeed distinct from the "neurogenic" phenotype of his brother. It has also been suggested that there is unlikely to be diagnostic difficulty in distinguishing type III SMA from limb girdle muscular dystrophy but case 1 shows that this may not hold true. We hope to raise awareness of the potential pitfalls in diagnosing type III SMA and the importance of molecular genetics in the diagnostic repertoire.

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Figure 1  (A) Patient 1. Top panel (haematoxylin and eosin stain): there is increased variation in fibre sizes, with hypertrophy of some fibres (histochemically type 2) and an increase in internal nuclei. Lower panel (acid phosphatase stain): there are frequent, scattered fibres undergoing necrosis, with granular cytoplasm and marked acid phosphatase staining indicating macrophage infiltration. (B) Patient 2. Top panel (NADH-TR stain): scattered, intensely staining, angulated fibres are seen. In contrast to patient 1, no necrotic fibres were seen and there was no increase in internal nuclei. Lower panel (NADH-TR stain): marked fibre type grouping is evident, but there is no grouped atrophy.
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