LETTERS TO THE EDITOR

A new form of infantile spinal muscular atrophy

We read with great interest the article by Borochowitz *et al*[1] describing a possible new form of infantile spinal muscular atrophy (SMA) characterised by congenital contractures, multiple bone fractures, and early death.

A few years ago we performed a detailed study of the skeletal changes in the long bones in 11 infants with neuromuscular diseases.[2] SMA was diagnosed at necropsy in six of these infants and these infants were clinically similar to the two patients reported by Borochowitz *et al*.[1] The infants with SMA in our study were from four families without parental consanguinity. The first three cases were consecutive offspring (two females and one male) of healthy parents, which provides additional support for the suggestion of Borochowitz *et al*[1] that this is an autosomal recessive disorder. The consistent radiographic findings of each infant with neuromuscular disease in our study were thin, hypomineralised, and elongated long bones. In addition, all infants with SMA showed multiple diaphyseal or metaphyseal fractures or both, primarily involving the long bones of the upper extremities. A morphometric evaluation of the long bones showed a more pronounced decrease in periosteal diameter, cortical thickness, and cortical area in the patients with SMA as compared to infants with other types of neuromuscular disease, for example, congenital myotonic dystrophy.[3] Since the shape and growth of bones are determined by an interactive process between the intrinsic properties of bone and biomechanical forces, severe fetal immobility can lead to hypoplastic bones and fragility. Moreover, stiff joints may play a role in the genesis of the fractures, owing to diminished absorption of the mechanical forces applied to the fragile bones during delivery and postnatal handling of the newborn.[2] Although in our experience joint contractures and bone fractures are non-specific findings, since they are related to the duration and severity of the intrauterine akinesia, their presence in infants with SMA probably implies a severe disorder of intrauterine onset. This assumption is further supported by the fact that many of the infants studied also had other abnormalities associated with fetal akinesia, such as polyhydrammios, intrauterine growth retardation, micrognathia, and pulmonary hypoplasia.[2] In conclusion, our previous studies support the suggestion of Borochowitz *et al*[1] of a new form of infantile SMA distinct from the common classical form of SMA I.

A GARCÍA-ALIX
J I RODRIGUEZ
J QUERO
Division of Neonatology, Hospital Infantil La Paz, Paseo de la Castellana 261, Madrid 28046, Spain.

1 Borochowitz Z, Glick B, Blazer S. Infantile spinal muscular atrophy (SMA) and multiple bone fractures in sibs: a lethal new syndrome. *J Med Genet* 1991;**28**:345–8.
2 Rodriguez JI, García-Alix A, Palacios J, Paniagua R. Changes in the long bones due tofetal immobility caused by neuromuscular disease. *J Bone Joint Surg (Am)* 1988; **70**:1052–60.
3 Rodriguez JI, Palacios J, García-Alix A, Pastor I, Paniagua R. Effects of immobilization on fetal bone development. A morphometric study in newborns with congenital neuromuscular diseases with intrauterine onset. *Calcif Tissue Int* 1988;**43**:335–9.

MASA syndrome (a form of complicated spastic paraplegia) and X linked hydrocephalus: variable expression of the same mutation at Xq28? Call for families

Spastic paraplegia is a common autosomal dominant disorder. In the complicated form, it may be present in combination with mental retardation or ophthalmological anomalies or both.[1] In the X linked recessive 'MASA' syndrome, the *S*pastic paraplegia is combined with *M*ental retardation, *A*phasia (late speech development), and *A*dducted thumbs.[2] We had the opportunity to examine two families where several males had either MASA syndrome or congenital hydrocephalus. Extensive data on both families have been previously published in this journal.[3,4]

Since the original description of MASA syndrome in 1974,[2] four other families have been reported.[5–8] Our family 1 was the first reported family that included males suffering from MASA syndrome, named as such, and X linked hydrocephalus (XLH). In this family the abnormality seen on CT scan of the brain was an important finding: the lateral ventricles were grossly enlarged and irregularly surrounded by brain tissue.[3] In families with XLH, surviving male relatives may present with (non-specific) mental retardation with or without spastic paraplegia.[9–13] The clinical findings of males with MASA syndrome are compared with mentally retarded males in families with XLH in the table. Although the clinical descriptions are not always extensive there seems to be an obvious clinical similarity.

Linkage analysis places the locus of both MASA syndrome and X linked congenital hydrocephalus on Xq28.[14] Thus, clinical data and DNA linkage analysis support the hypothesis that MASA syndrome and X linked hydrocephalus are variable expressions of the same mutation at Xq28.

We would like to make a call for families with (possible) MASA syndrome, with or without male relatives with XLH, for further delineation of the clinical spectrum and understanding of the genetic basis. With a diagnosis in hitherto undiagnosed mentally retarded males it will be possible to provide adequate genetic counselling to the families. Female relatives at risk may benefit from the possibilities of prenatal diagnosis.

C SCHRANDER-STUMPEL
Department of Clinical Genetics, University of Limburg, PO Box 1475, 6201 BL Maastricht, The Netherlands.
J P FRYNS
J J CASSIMAN
E LEGIUS
A SPAEPEN
Centre for Human Genetics, University of Leuven, Herestraat 49, B300 Leuven, Belgium.
C J HOWELER
Department of Neurology, University of Limburg, 6200 AZ Maastricht, The Netherlands.

1 Harding AE. *The hereditary ataxias and related disorders*. Edinburgh: Churchill Livingstone, 1984:174–204.
2 Bianchine JW, Lewis RC Jr. The MASA syndrome: a new heritable mental retardation syndrome. *Clin Genet* 1974;5:298–306.
3 Schrander-Stumpel C, Legius E, Fryns JP, Cassiman JJ. MASA syndrome: new clinical features and linkage analysis using DNA probes. *J Med Genet* 1990;**27**:688–92.
4 Fryns JP, Spaepen A, Cassiman JJ, Van den Berghe H. X linked complicated spastic paraplegia, MASA syndrome, and X linked hydrocephalus owing to congenital stenosis of the aqueduct of Sylvius: variable expression of the same mutation at Xq28. *J Med Genet* 1991;**28**:429–31.
5 Gareis F, Mason JD. X linked mental retardation associated with bilateral clasp thumb anomaly. *Am J Med Genet* 1984;**17**:333–8.
6 Yeatman GW. Mental retardation-clasped thumb syndrome. *Am J Med Genet* 1984; **17**:339–43.
7 Kenwrick S, Ionasescu V, Ionasescu G, *et al*. Linkage studies of X linked recessive spastic paraplegia using DNA probes. *Hum Genet* 1986;**73**:264–6.
8 Winter RM, Davies K, Bell MV, *et al*. MASA syndrome: further clinical delineation and chromosomal location. *Hum Genet* 1989; **82**:367–70.
9 Edwards JH. The syndrome of sex-linked hydrocephalus. *Arch Dis Child* 1961;**36**:486–93.
10 Fried K. X linked mental retardation and/or hydrocephalus. *Clin Genet* 1972;**3**:258–63.
11 Halliday J, Chow CW, Wallace D, *et al*. X linked hydrocephalus: a survey of a 20 year period in Victoria, Australia. *J Med Genet* 1986;**23**:23–31.
12 Willems PJ, Brouwer OF, Dijkstra I, *et al*. X linked hydrocephalus. *Am J Med Genet* 1987;**27**:921–8.
13 Kelley RI, Mennuti MT, Hickey WF, *et al*. X linked recessive aqueductal stenosis without macrocephaly. *Clin Genet* 1988;**33**:390–4.
14 Willems PJ, Dijkstra I, Van der Auwerda BJ, *et al*. Assignment of X linked hydrocephalus to Xq28 by linkage analysis. *Genomics* 1990; **8**:867–70.

Clinical comparison between male patients with MASA syndrome and mentally retarded males from families with X linked hydrocephalus.

Clinical features	MASA males[2–8] (n = 22)	XLH males[9–13] (n = 20)
Head circumference (centile)	10th–98th	10th–>98th
Mental development (IQ)	40–75	20–50
Adducted thumbs	18/22	8/14
Spastic paraplegia (hyperreflexia)	17/17	19/20
Abnormal CT scan of the brain (enlargement of the ventricles)	2/3	5/7