LETTERS TO THE EDITOR

Hypoglossia-hypodactyly syndrome with hydrocephalus

We note with interest the report by Gillerot *et al*¹ suggesting that a case of hypoglossia-hypodactyly syndrome with hydrocephalus was caused by an acquired inflammatory process. The authors indicate that their case was an example of Hanhart's syndrome.

The histopathology in the brain stem of their case is very similar and probably identical to that reported in two cases of Moebius syndrome reported by ourselves and by a variety of other authors documented in that paper.² Although two cases in our series were associated with high fever, one with pneumonitis and the other with an abscessed wisdom tooth, an observation confirmed by Graham *et al*³ at a similar gestational stage, there is no evidence that these infections involved the fetus or membranes, and ample evidence of a uteroplacental insufficiency aetiology with association of electric shock, failed abortion, prolonged rupture of the membranes, previous uterine surgery, and alcohol abuse as well as hyperthermia. A rat animal model in which the uterine artery is occluded or handled and the uterus itself handled, in addition to systemic administration of cocaine, results in similar brain stem lesions.^{4,5} Other animal experimentation includes the work of Miller and Myers,⁶ who simultaneously occluded the major vessels of adult rhesus monkeys for a measured length of time. During arrest of systemic flow, the pulmonary and coronary vessels remained unobstructed allowing the passage of oxygenating blood through the lungs and heart. The animals, who did not have significant post arrest hypotension, had a typical pattern of brain stem ischaemia and necrosis. Ranck and Windle⁷ caused asphyxia in near term *Macaca mulatta* by detaching the placenta at hysterotomy and keeping the fetal membranes intact. A pattern of brain stem injury, affecting the cranial nerve nuclei in particular, was observed. Further analysis of human material indicates that similar brain stem lesions, while sparing the cerebrum, could occur after resuscitation for cardiac arrest in the perinatal and even in the adult patient.^{8,9} These case series and animal experiments are consistent with Bouwes-Bavinck and Weaver's hypothesis¹⁰ that the Moebius and other oromandibular-hypogenesis syndromes, including Hanhart's and hypoglossia-hypodactyly syndromes, result from interruption of embryonic blood supply with the extent and nature of the associated defects dependent on the specific location of vascular insufficiency. Added credence to the case series, animal experimentation, and the above hypothesis is given in cases of oromandibular-limb hypogenesis syndrome, including the Moebius syndrome, after chorionic villus sampling at 56 to 66 days' gestation.¹¹ The authors' contention that drug intake

during pregnancy could be associated is probably misdirected. The drugs associated with their articles were Meclizine, an antihistamine drug, and Bendectin, which have been shown to be non-teratogenic. The consanguinity noted by them in previous reports is also probably coincidental, although congenital seventh and sixth nerve palsies unassociated with limb deficiency have been well recorded in some cases to be monogenic in nature, either autosomal dominant or X linked recessive.^{12,13}

We would also wish to draw attention to previous correspondence on this issue in this Journal in 1990.¹³

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Fragile X syndrome: as common as first thought?

The recent letter by Webb and Bunday¹ concerning the prevalence of fragile X syndrome noted similar findings to those seen in

this laboratory. For some years there has been a marked decrease in the number of confirmed fragile X cases in this area and I have concluded that the incidence in the general population is not as high as the figure usually quoted (that is, in the region of 1 in 1000).

This laboratory began routine screening for fragile X during 1980 and in the 10 year period from 1981 to 1990 a total of 47 positive cases was identified. Forty-three of these were from families with a history of X linked mental retardation, including 13 cases from one large kindred.² Only four patients with no family history were positive.

In the first three years of the study most of the referrals were from the families with a positive history. However, after the initial interest waned, and recall of patients seen before the discovery of the fragile X chromosome ceased, the number dropped dramatically to be replaced by a majority of single case referrals. Overall, the incidence of positive fragile X cases was noted in 33.5% of the total referrals. Only 2.2% of the single case referrals were positive compared with 32.8% of the familial cases. The number of positive cases peaked in 1983 and have fallen off since then. Only one case was detected in 1988 and one case in 1989. There were no positive cases in 1990.

The number of births in the Cape Town hospital area is approximately 25 000 per annum. In the 10 year period studied, 250 000 children were in the age group for referral. If the incidence is taken as 1 in 1000 we would have expected 250 cases of fragile X over this period. Only 47 cases were detected.

The question asked by Webb and Bunday¹ was whether the incidence of fragile X had fallen off, or was more education of hospital staff required. In our situation the majority of referrals are from hospital clinics (neurology, developmental clinic, and our own genetic clinics where the staff has remained fairly stable during the time period in question. It would seem more likely that the original rush of enthusiasm which heralded this condition also produced a falsely raised incidence based on the initial positive chromosome results.

In my own experience an incidence of 1 in 5500 would be a more accurate figure, based on the positive results compared with the population. As there are also a great number of home deliveries in this region which are hard to monitor, the figures I have quoted are approximate but would, if anything, serve to produce an even lower incidence than I have estimated. It would be interesting and informative if other centres could estimate an incidence figure for their region based on positive chromosome results over a specific time span in relation to the population in their area.

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