Correspondence

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Amylase polymorphism

Sir,

Tye et al. (1976) conclude that some of our earlier findings (Kamaryt and Fintajslová, 1970) obtained by agar gel electrophoresis of human amylase are misleading and incorrect. In particular they challenge our results on the ratios of salivary to pancreatic amylase in children.

We estimated that the ratio of salivary to pancreatic amylase in blood serum (not in urine) from children up to 1 year old is about 2:1. In blood serum from adults the ratio is about 1:1, whereas in urine it is 1:2. The relatively higher levels of pancreatic amylase in urine are probably a consequence of the higher renal clearance of this type of amylase (Kamaryt, 1969).

Tye et al. appear to have confused things by comparing their own results obtained by polyacrylamide gel electrophoresis of urine samples with our results on blood serum. In addition they conclude that our electrophoretic separation on agar did not distinguish the salivary and pancreatic amylases. They suggested that overlapping pancreatic isoenzymes were scored as salivary amylase, thus leading to an overestimate of the salivary and an underestimate of the pancreatic amylase isoenzymes. However, we never did observe such an overlap under our experimental conditions of agar gel electrophoresis. The root of this discrepancy appears to be in comparing our results obtained from blood with their results from urine. Furthermore the differences in the rates of renal clearance between the two amylase isoenzymes do not appear to have been taken into account in the analysis of Tye et al.

Yours, etc,

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Autosomal dominant trigonocephaly

Sir,

The recent discussion of autosomal dominant trigonocephaly associated with minor anomalies by Hunter et al. (1976) is disturbingly misleading to readers unfamiliar with the variable expression of the craniosynostosis syndromes.

The authors reported on a 6-month-old male child who ‘... had trigonocephaly with prominent metopic ridge, shallow orbits, epicanthic folds, and minimal ptosis. ...’ There was ulnar deviation of the terminal phalanges of the first and second digits of the hands, and bilateral clinodactyly of the fifth fingers. The right hallux was extremely broad. ... Dermatoglyphic studies revealed a low total ridge count (44) ... There was duplication of the distal phalanx of the right hallux ...’. Total craniosynostosis was also reported by the authors.

The mother of this patient had a ‘... head circumference of 51 cm (below 3%) ... pronounced oxycephaly with tall narrow forehead with a prominent bulge at the bregma and a low straight anterior hairline; ... maxilla was hypoplastic and the entire face was concave to the right. She had exaggerated cervicothoracic kyphosis ... Dermatoglyphics revealed a low total ridge count (56). ...’ A maternal uncle of the mother was ‘reported to have pronounced cutaneous syndactyly and similar curvature of the fingers ...’.

The authors evidently were misled by the mild involvement of these patients and failed to identify their patients’ condition as one of a group of more severe malformations which has not occurred to them yet the ‘acrocephalosyndactyly syndromes’ (ACS). McKusick (1975) recognises 5 types which range from a very severe form, Apert syndrome (ACS Type I), to a mild form, the Saethre-Chotzen syndrome (ACS Type III). Pantke et al. (1975) have characterised the latter as an autosomal dominant trait with variable expressivity presenting craniosynostosis, acrocephaly, low-set frontal hairline, facial asymmetry, ptosis of the eyelids, deviated nasal septum, partial cutaneous syndactyly of hands and feet. Pruzensky et al. (1975) have shown a patient who also had broad halluces with duplicated distal phalanges.

The findings in Hunter et al.’s patients are clearly those of patients with the Saethre-Chotzen syndrome and the proband’s mother’s pictures are highly

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suggestive of this diagnosis. From the photographs I suspect the mother has acrobrachycephaly and the reported trigonocephaly only represents involvement of the metopic suture as part of the generalised type of craniosynostosis seen in the Saethre-Chotzen syndrome. The facial resemblance with Chotzen’s original patients is extraordinary (Chotzen, 1932).

Recently I have reviewed the published material on autosomal dominant trigonocephaly, and it is my opinion that the patients reported by Hunter et al. represent examples of this familial trait (ACS type III) and have an increased risk of producing children with a more severe form of ACS. Dr David Bixler and myself have suggested (1976a) that the ACS syndromes are the result of a single gene mutation and can occur in the same family. A characteristic metacarpophalangeal analysis (Escobar and Bixler, 1976b) does not discriminate among these disorders. Jackson et al. (1976) have shown a family which confirms our suspicion that a single gene defect is responsible for ACS types I, III, and V (McKusick’s classification, 1975). ACS type II has been shown to represent a variant of ACS type I, and ACS type IV is of dubious existence.

Yours, etc,

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This letter was shown to Drs Hunter and Rudd who reply as follows:

Sir,

Thank you for the opportunity to reply to the letter of V. Escobar. The main points of his letter appear to be that he believes that our patients represent acrocephalo-syndactyly type III (ACS type III or Chotzen syndrome), and that he further argues that ACS types I, III, and V are the result of a single autosomal dominant gene. In support of the latter point he refers to the paper by Jackson et al. (1976) in which the authors specifically state that no patients with ACS type I were seen and that thumb abnormalities were not a feature of this syndrome. He further states that ACS type II has been shown to be a variant of ACS type V. In fact, the original patients with ACS type II reported by Vogt (1933) are far more likely to represent a variant of ACS type 1, and we suspect that he means to refer to the belief that acrocephalopolysyndactyly type I (Noack syndrome) is felt by some writers to represent the ACS type V (Pfeiffer) syndrome (McKusick, 1975, pp. 5-6). This latter conclusion is based on the description of a child born subsequently into the original family reported by Noack (Pfeiffer, 1969). However, this patient had 6 metatarsals on each foot which is not a feature of ACS type V as originally described by Pfeiffer (1964). The identity of the Noack and Pfeiffer genes is unproven.

Despite these confusions, Dr Escobar’s letter does serve to illustrate the challenging issues confronting those interested in the nosology of craniosynostosis. Clearly there are families showing considerable variation in clinical features, but this in itself does not preclude the possibility of several ‘craniosynostosis’ genes or even allelic mutants of the same gene. For example, Cohen (1975) in a recent review has chosen to maintain the identity of the various craniosynostosis syndromes. We have recently reviewed the history of 370 patients with craniosynostosis (Hunter and Rudd, 1976, 1977). A number of families have shown typical ACS syndromes and others appear to represent quite distinct ‘private syndromes’. Space
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does not permit full discussion of these families but suffice it to say that the genetics of the various craniostenoses are unlikely to be as simple as Dr Escobar might wish to think.

We agree that the mother of our patient shows many of the features in adulthood of the other ACS syndromes and in particular ACS type III. However, as infants, both patients presented with clear-cut trigonocephaly and lacked the soft tissue syndactyly seen in Chotzen syndrome. Certainly neither patient would have been recognised as a case of Chotzen syndrome or any of the other ACS syndromes in the newborn period. Therefore, had either of these infants been seen for genetic counselling in the absence of a positive family history, there would have been no rationale for counselling on the basis of an autosomal dominant gene. At present there is no information as to the frequency with which isolated craniosynostosis represents new dominant mutations. We, therefore, felt it important to report autosomal dominant trigonocephaly and in particular to emphasise the importance of minor acroskeletal anomalies in distinguishing the familial cases. The importance of these minor anomalies has been proven to be useful in other families multiply affected by craniosynostosis (Hunter and Rudd, 1977). Our patients are clearly not typical examples of the Chotzen syndrome and whether or not they represent variable expression of the Chotzen syndrome gene, or a mutation, either allelic or at a different locus cannot be determined from the current state of knowledge. Observation of the experiences of biochemical geneticists should lead us to expect genetic heterogeneity in craniosynostosis, with or without associated syndactyly or poly-syndactyly.

Yours, etc,

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References


Risk of closed lesions in sibs of cases of open neural tube defect

Sir,

Recent studies (Wynne Davies, 1975; Carter et al., 1976) have shown that malformations resulting from defective closure of the neural tube cover a spectrum ranging from spina bifida occulta through open meningomyelocele to anencephaly.

Families at risk for the recurrence of neural tube defects may have a child with any degree of the abnormality, or one with hydrocephalus alone (Lorber and Ne, 1970). Alpha fetoprotein (AFP) in amniotic fluid is recognised as a reliable index of open neural tube defect in the fetus (Brock and Sutcliffe, 1972), allowing selective termination of potentially handicapped children.

Two cases of true closed lesions occurred in 12 recurrences in the first 140 pregnancies ‘at risk’ for recurrence of neural tube defect in N.S.W., Australia. The previous abnormality was spina bifida in 91 cases and anencephalus in 49 cases.

Both cases described showed no evidence of abnormality on antenatal testing (serial echograms, serum, and amniotic fluid AFP at 15 to 16 weeks of pregnancy). The previous sib had died after conservative management of severe open thoracolumbar meningomyelocele in each instance.

The first case, a female, was noted at birth to have a mobile swelling to the left of midline in the inner quadrant of the buttock. There was no neurological deficit. X-ray pictures of the spine were reported as normal. Myelogram at 15 months showed a sacral meningocoele with tethered cord. Excision of the lipoma, and freeing of the cord were performed and the child is developing normally.

The second, a male, was noted at birth to have a head circumference of 39.4 cm, which increased rapidly to 44.3 cm at 3 weeks of age. Investigation by air ventriculogram showed moderate hydrocephalus with pronounced asymmetry, the left lateral ventricle smaller than the right, displacing the septum pellucidum across the midline. A large paraventricular cyst stretched from vertex to occiput region on the left side and the blockage was at aqueduct level. A ventriculoperitoneal shunt was inserted. The head circumference is continuing to increase, and at 5 months he is showing delay in developmental milestones.
Autosomal dominant trigonocephaly.

V H Escobar

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