Triphalangeal thumb with delta phalanx in a case of Klinefelter’s syndrome

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Abstract
We report a case of Klinefelter’s syndrome owing to maternal meiotic error associated with triphalangeal thumb and delta phalanx bilaterally. There are no previous reports of similar cases and triphalangism with delta phalanx abnormalities of both thumbs might therefore be considered a further, but rare, manifestation of this aneuploidy.

Triphalangeal thumb (TPT) is a rare condition characterised by the interposition of an extra phalanx between the two normal phalanges of the thumb. Three characteristic types of extra bone in the thumb can be found. One type consists of complete hyperphalangism with three normal appearing phalanges and joints. The thumb usually appears excessively long. In the second type, the extra middle phalanx is small, triangular in shape, and is called delta phalanx. The proximal epiphysis is C shaped rather than straight and tends to lie on the shorter side of the abnormal bone. The peculiar arrangement of this epiphysis makes longitudinal growth of the digit impossible and causes an angular deformity so that the thumb appears bent inwards toward the index finger. A third type consists of a regular finger containing three phalanges that takes the place of the thumb, as suggested by the analysis of the dermatoglyphics.

Three hypotheses have been put forward to explain TPT. TPT could arise from the presence of a middle phalanx owing to the failure of fusion of the terminal and middle phalanges. Secondly, TPT may be considered a duplication of the index finger which replaces an absent thumb. The third hypothesis suggests that TPT could be the result of an attempt at formation of a bifid thumb, the supernumerary phalanx representing the base of the bifid thumb. Triphalangeal thumb can occur either as an isolated defect or as a feature of several rare malformation syndromes. We describe a case with TPT which we found on investigation to be associated with Klinefelter’s syndrome.

Case report
The proband, a 2 year old boy, was the first child of non-consanguineous parents. The mother was 25 and the father 30 years of age at the time of his birth. They had no physical abnormalities, neither did other members of their families. The father suffered from Christmas disease (factor IX deficiency). The mother was eight weeks pregnant with a second child at the time of referral. The proband was born after an unremarkable pregnancy during which no medication was taken and the birth weight was 3000 g. A flexed thumb with 70° of ulnar angulatory deformity was present in both hands and noted at birth. It was this extreme deformity that led to the referral by the Hand Clinic at Lewisham Hospital to the SE Thames Regional Genetics Centre, Guy’s Hospital, London SE1 9RT.

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Genetic Centre in order to ascertain whether there were any genetic implications of this deformity.

Physical examination at 2 years of age showed a lively child with height on the 10th centile and head circumference on the 3rd centile. The thumb deformities were as described and x-rays showed an additional middle phalanx with a delta deformity in each of the thumbs (figure). There were no other dysmorphic features; heart sounds were normal, and he had no café au lait patches. Developmental assessment showed him to have a marked speech delay.

LABORATORY FINDINGS

Since abnormalities of the thumb are a frequent feature of Fanconi’s anaemia, a recessive disorder for which prenatal diagnosis would be available for the pregnant mother, an analysis of the susceptibility to chromosome breakage by mitomycin C was performed on the proband. No evidence of excessive breakage was found and Fanconi’s anaemia was therefore ruled out. However, routine chromosome analysis indicated Klinefelter’s syndrome (47,XXY).

In view of the haematological disorder present in the father and the chromosome complement of the proband, we measured the factor IX levels of the proband which were found to be in the normal range. This did not exclude heterozygosity for haemophilia B, such as would occur if the chromosome abnormality had occurred at paternal gametogenesis. We therefore characterised the factor IX mutation in the patient’s father by the rapid procedures developed in our laboratory. This revealed a leucine (330)-proline substitution owing to a T to C transition at position 31110. Such a mutation was absent in the DNA of the proband who must therefore have inherited his two X chromosomes from his mother. Unfortunately, the RFLP analysis to determine at which meiotic division the non-disjunction occurred was uninformative.

Discussion

The proband shows the combination of bilateral triphalangeal thumb with delta phalanx and Klinefelter’s syndrome (47,XXY). Isolated TPT is bilateral in 90% of cases and both sexes are equally affected. TPT is often associated with other anomalies, such as polydactyly of the thumb or big toe, cleft feet, patella dislocation, radial hypoplasia, onychodystrophy, imperforate anus, defects of the tibia, cleft palate, congenital heart disease, and particularly Holt-Oram syndrome. TPT has also been observed in Fanconi’s pancytopenia, Blackfan-Diamond anaemia, and hypoplastic anaemia. On rare occasions it has been reported in trisomy 13, in Joubert-Hayward syndrome, and as a result of maternal exposure to teratogens such as hydantoins and thalidomide.

The delta phalanx most commonly occurs in the extra phalanx of the triphalangeal thumb and in the little finger. It has also been found in metacarpals and metatarsals. It can occur as an isolated defect or in combination with triphalangeal thumb or many other abnormalities such as syndactyly, polydactyly, symphalangism, cleft foot, cleft hand, ulnar club hand, Apert’s syndrome, Poland’s syndrome, Larsen’s syndrome, diastrophic dwarfism, broad thumb syndrome, Holt-Oram syndrome, and Rubinstein-Taybi syndrome.

Klinefelter’s syndrome occurs with a frequency of 1 in 2000 live births and it is associated with an increase in maternal age. According to Jacobs et al., 53% of the non-disjunctions are attributable to paternal meiotic first division errors, 34% to maternal meiotic first division errors, 9% to maternal meiotic second division errors, and 3% to a postzygotic mitotic error.

Our proband does not have any of the other features previously described in association with triphalangeal thumb. Other skeletal abnormalities of the upper limbs, in particular radioulnar synostosis, are well recognised as occurring in Klinefelter’s syndrome, but as far as we are aware there are no previous reports of any association with triphalangeal thumbs. We wonder whether triphalangism with delta phalanx can be considered a further manifestation of Klinefelter’s syndrome. It has been suggested that the parental origin of the chromosomal abnormality might affect the phenotype of the resulting offspring.

In this case, the triphalangeal thumb has occurred in a child with a chromosome complement of 47,XXY which has arisen from a maternal meiotic error. It would be interesting to see if radioulnar synostosis has any greater tendency to occur in cases which have arisen by maternal rather than paternal non-disjunction.