

CASE REPORT

Study of three non-syndromic cases of congenital thumb aplasia in captive rhesus monkeys

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Abstract

Although congenital thumb absence has been reported frequently in humans, their occurrence in macaques is rare. We observed three cases of spontaneous thumb defects in captive female rhesus monkeys. One animal exhibited bilateral absence and two other presented unilateral thumb absence, all with metacarpal integrity. This report presents the clinical, radiological, and genealogical details as well as possible etiologies in an attempt to draw a parallel with humans and other primate species.

Introduction

Congenital defects represent a complex and heterogeneous group of embryonic and / or fetal disorders that around 50% of cases have no known cause. Those caused by genetic factors are the most well known and include monogenic, chromosome, and multifactorial causes. Rhesus monkeys have been extensively used as a model for human disease including teratology research [22]. The evaluation of the type and incidence of congenital anomalies in colonies of laboratory non-human primates (NHP) is important to own creation and as a model for human anomalies. Experimental induction causing malformations in NHP proved the importance of its use as a model for the study of birth defects, as well as screening of potential teratogens before human exposure [14]. Constant monitoring of these spontaneous events is also important in understanding trends and patterns to identify potential defects. The estimated incidence of congenital malformations in captive colonies is difficult because small defects of little clinical significance can be neglected, autopsies are not always performed and internal changes often unnoticed. Reports of these natural birth defects are important in assessing the effectiveness of exogenous teratogens,

toxicity of drugs and industrial chemicals, assessment of virus-induced malformations testing, and understanding the genetic changes [30]. Hand development occurs simultaneously with the growth and development of the cardiovascular, neurologic, and hematopoietic systems. Therefore, congenital anomalies seen in the hands of infants may indicate significant anomalies in these other systems, requiring a comprehensive physical evaluation [3]. Congenital thumb defects can range from a slight decrease in size to complete absence [17]. Hypoplastic thumb is commonly associated with radial dysplasia, occurring in 1 of every 100,000 human births, being bilateral in over 50% of patients. In a study of 98 human patients with hypoplastic thumb, it was observed that 86% had other deficiencies and 59% had radial dysplasia [16]. The incidence of thumb hypoplasia is estimated to be almost 4% of all congenital anomalies of the hand [12, 16]. Congenital aplasia of the hallux (big toe) was observed in seven adult and infant members of a free-ranging group of silvery marmosets (*Mico argentatus*) as an isolated feature. The condition was observed on one or both feet in different individuals, with absence or partial deformation of the hallux. Apparently heritable, the condition was more common in males (80%) than females (50%). Despite the

potential connotations of the condition, the individuals affected appeared able to survive to adulthood and reproduce [10]. The absence of thumbs associated with bilateral radial aplasia was related to *Aotus nancymae* [23] and to squirrel monkey [13] together with other defects. Five degrees of thumb hypoplasia has been classified [5]. Type 5 hypoplasia (absent thumb) represents the majority, reported as approximately one-third of all cases of thumb hypoplasia [12, 16]. The aim of this study was to describe three cases of thumb absence presenting in a colony of captive rhesus monkeys, drawing a parallel with the findings in humans in an attempt to shed some light on their etiologic heterogeneity, a characteristic feature of birth defects.

Case report

Three rhesus female monkeys (*Macaca mulatta*) born in the Center for Laboratory Animal Breeding from Oswaldo Cruz Foundation, Rio de Janeiro, Brazil with isolated thumb absence were identified during the annual clinical management of the colonies in year 2013.

Case 1 – Female, 2 years old presenting complete absence of the left thumb (Fig. 1A).

Case 2 – Female, 12 years old presenting congenital absence of the right thumb (Fig. 1B). According to the clinical records of the animal, other finger injuries evidenced in radiography are due to amputations during fights.

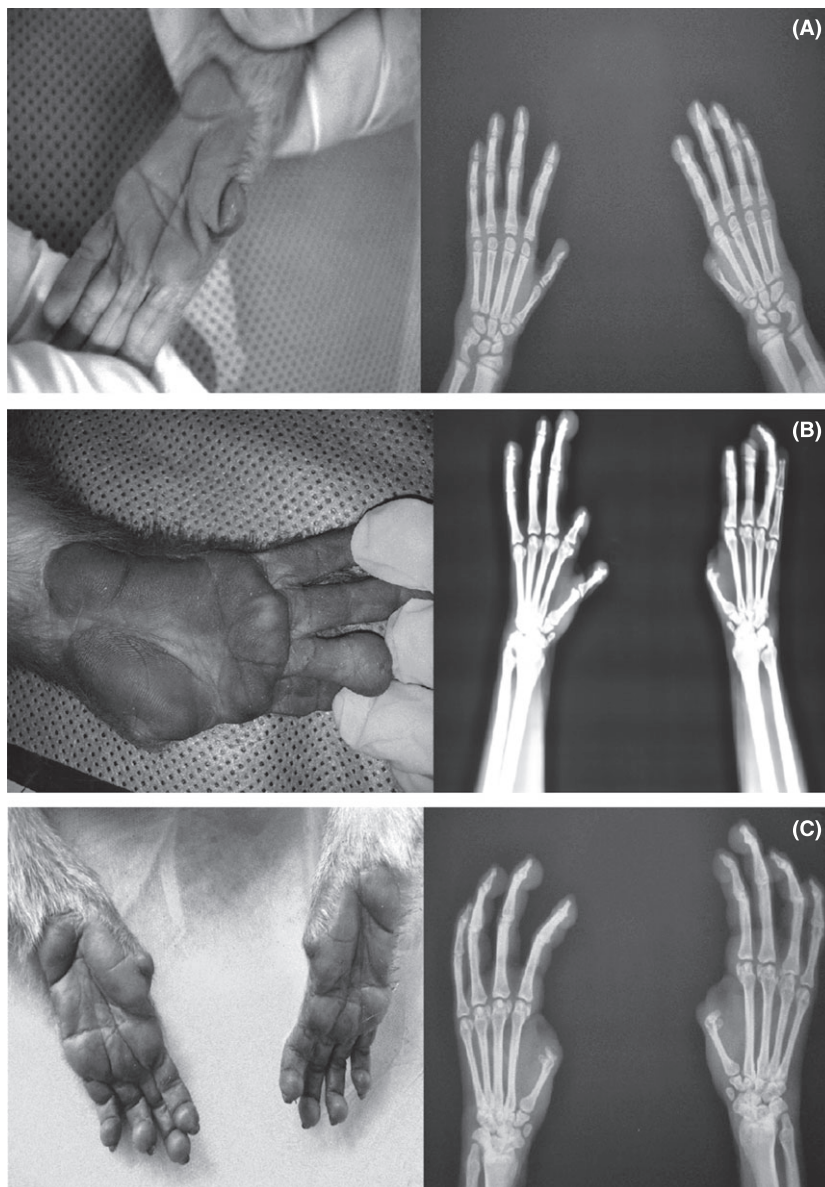


Fig. 1 Photography and radiography of the hands of a female rhesus monkey showing congenital aplasia of the left thumb in case 1 (A); female rhesus monkey showing congenital aplasia of the right thumb. Other digit of both hands showing amputations is due to fights in case 2 (B); female rhesus monkey showing congenital bilateral aplasia of the thumbs in case 3 (C).

Case 3 – Female aged fourteen with congenital absence of both thumbs. By pedigree analysis, there was no evidence of inbreeding. It gave birth to eight unaffected offspring and one more male with agenesis of the distal phalanx of the third finger in both hands and not described here (Fig. 1C).

Cases 1 and 2 are sister by mother. All three cases fall under the classification of Blauth [5] as Type V. No chromosomal abnormality was observed in any case, and blood count of all animals was within the normal standard [2]. Radiographic images of the complete absence of thumb, both for single and bilateral, showed agenesis of the distal and proximal phalanges and metacarpal integrity.

The rhesus macaques in this colony live in single male breeding groups of 20–25 animals in cages of 48 m², receive filtered, treated water *ad libitum* through automatic stainless steel waterers, and fed a commercial primate chow (Nuvilab Primates 6030; Nuvitab, Colombo, Brazil) in the morning, supplemented with fruits and vegetables in the afternoon, which first were immersed in a 2% sodium hypochlorite solution for parasitological and bacteriologic control. The enclosures is swept clean daily and washed with pressurized water three times each week; no chemical is used. Each enclosure has perches, drums, trunks of trees, swings, and environmental enrichment items (offering of fruit sorbet, popcorn, tire swing, and pool on hot days). It has a covered part, which serves as a shelter or refuge containing a stainless steel feeder. The enclosures are located in natural lighting environment with no controlled ambient temperature. The clinical and behavioral histories of these animals are stored in individual files containing records such as birth date, housing conditions, diet, drug exposure, diseases, traumas, and surgeries. Pedigrees were constructed to rule out history of any congenital anomaly, the consequent level of inbreeding and the mode of inheritance. Photographs and radiographs of affected hands of all subjects were obtained. Blood was collected from the femoral vein with EDTA for cell count and with sodium heparin for preparation of peripheral blood cells for chromosome analysis. The breeding colony is maintained in compliance with Brazilian law and approved by the Ethics Commission on Animal Experimentation of the Oswaldo Cruz Foundation under protocol number LW-24/09.

Discussion

Absent thumbs occur in many syndromes and are a signal for careful examination, as some can occur as an isolated deformity or in association with several

syndromes. It can also be seen with brachydactyly and other preaxial deficiencies [6]. Thumb hypoplasia occurs when the structures on the radial side of the forearm fail to develop normally. The underlying cause of these anomalies is unknown, although signals from the zone of polarizing activity in the vertebrate limb bud are known to control the pattern of cellular differentiation in a radioulnar direction [21, 27]. Blauth classification system has been used to outline hypoplastic thumbs into five degrees which depict increasing severity of deficiency. Hypoplastic thumb in humans is described more often in males than in females and is bilateral in about two-third of the cases [9, 16, 26]. Most of the isolated cases of absent thumb are sporadic. Here, the cases of thumb aplasia described are all in females. It is generally accepted that the incidence of offspring with malformations is about twice as high among consanguineous than among non-consanguineous couples [11, 25]. Within this sample, the hand anomaly is similar in both cases 1 and 2, but on the opposite side. They are sister by mother, representing a high level of consanguinity, which would indicate a common genetic origin for the condition, even with the same expressiveness and difference in laterality. This finding was interpreted as a developmental field defect that is a group of embryonic cells that develop together as a single unit with autosomal dominant transmission. The molecular etiology of thumb hypoplasia/aplasia remains less described [16], but the fact that no chromosomal abnormalities have been found does not mean that there are no molecular changes under 3–5 kb. The genetic basis of several syndromic forms of first digital ray deficiency has been discovered such as Fanconi anemia [28], where approximately 50% of patients are born with abnormalities of the thumb and radio. It is recommended that all patients who are born with abnormalities of the thumb are investigated [29]. Holt-Oram is an autosomal dominant malformation syndrome [8, 15], where affected individuals have bone changes in the upper limbs, pectoral hypoplasia, and cardiovascular changes. Affected patients may present with agenesis or hypoplasia of thumbs, trisphalangia, syndactyly, among others [19]. VACTERL is a set of anomalies that have vertebral abnormalities, anal atresia, cardiovascular, tracheoesophageal, renal anomalies, and changes in members [4]. Nager is a rare and complex malformation characterized by abnormalities in ears, micrognathia, radial hypoplasia, and fingers aplasia [20], but none presents isolated absent thumb. The MSX family comprises MSX1 and MSX2 homeobox containing genes, which are important developmental regulators involved in the processes of limb, craniofacial, and ectoderm formation in vertebrates [1]. Based on the observation

of a 5q tetrasomy carrying human patient, it has been hypothesized that multiple copies of 5q (including MSX2) result in a more severe skeletal anomaly such as absent thumbs [24]. While most congenital defects of the limbs in non-human primates are related to specific physiological circumstances or environmental factors [7, 18, 23], the condition recorded here appeared to be heritable the same way as described for free-ranging silvery marmosets (*Mico argentatus*) with congenital digital aplasia of the hallux [10]. There is so far no specific genetic factor known for isolated thumb aplasia, compromising an accurate genetic counseling. Collection of patients with similar phenotypic presentations could be useful in further molecular genetics investigations. The animals here presented underwent hemogram with blood collected by femoral venipuncture as a standard reference [2] to captive rhesus monkeys. No change was found. The radiographs performed had no other

changes besides the absence of thumb. Cytogenetic evaluation ruled out the presence of changes that characterize a specific syndrome. Thus, the suspicion that the cases fit into any of the aforementioned syndromes was discarded. No animal in the colony had contact with any chemicals that may have caused the congenital abnormalities described. However, cases 1 and 2 showed a high level of consanguinity, and case 3 had a descendant also carrier of digital defect, suggesting a heritable etiology for this condition in these monkeys. Although this observation gives no certainty as to etiology in individual cases, it should be a useful tool when studies on genetic markers or candidate genes are being considered.

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