15 March 2005

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Pachyonychia congenita-like disorder in cotton-top tamarins (Saguinus oedipus oedipus)


A spontaneous genodermatosis in 13 cotton-top tamarins is described as a retrospective study. The disease appeared as alopecia, pigmented disturbances, and claw dystrophy similar but not identical to human Pachyonychia congenita. The disease in the tamarins seems to be inherited as an autosomal recessive trait, becoming clinically apparent around adolescence. In certain families the neonatal mortality rate was also above average, reaching 100%.

Introduction

The German Primate Center (Deutsches Primatenzentrum, or DPZ) acquired a cotton-top tamarin (S. o. oedipus) colony of 83 animals in 1978 from another institute where the animals were used in virological experiments on simian herpesviruses [16-18]. Neither the individual experimental data nor the genetic background of that parental generation were provided. Some animals most certainly were wild-caught, others were born in captivity. The record-keeping on the animals started only after the colony's takeover by the DPZ, where they are used exclusively by the working group “ethology,” which is also in charge of all management. Dead or seriously ill animals are submitted to the pathology department for necropsy following sacrifice.

The following report therefore focuses on the retrospective evaluation of routine necropsies, but is by no means the result of a planned breeding project. Among the cotton-top tamarins that died or had to be sacrificed for humane reasons were several that suffered from a severe epidermic syndrome affecting the skin, the haircoat, the claws, and, in case of the first toes, the toenails. The affected animals were born with a normal neonatal haircoat that developed to a normal infant's pelage. During late infancy, adolescence, or early adulthood thinning of the body hairs was noted, although neither increased shedding of hair nor any pustular, vesicular, or crusty skin diseases were noted at any time. Simultaneously, gross elongation, decoloration, and twisting of some of all claws or, in the case of the first toes, of the nails became obvious and in some cases necessitated the animal's sacrifice because of increasing walking and climbing problems, which in turn interfered with the behavioral studies.

Materials and methods

Since record-keeping began at the DPZ, a total of 13 animals were observed to suffer from this disease. Two more somewhat similar fatalities in adults animals shortly after acquisition of the colony could not be included owing to the lack of background information, certain technical problems, and the lack of breeding success, resulting in the genetic loss of both animals.

Eighteen animals had to be destroyed for humane reasons, accomplished by barbiturate overdosage after an initial ketamin-sedation (Ketanest—15 mg/kg, Parke Davis, CA). Blood samples were taken during the initial sedation and the necropsies were performed as soon as possible after the animals' death. Specimens for mycology and bacteriology were taken from affected skin and nails and from the abdominal and thoracic organs, but because they did not provide etiological clues they will not be discussed further. Virological examinations were and still are not possible because the DPZ lacks a diagnostic virology department. For histopathology, specimens from all abdominal and thoracic organs, the brain, skin, and claws were routinely fixed in 10% neutral-buffered formalin and paraaffin embedded, except the claws, which were embedded in low temperature—polymerizing resin (Technovit, Kulzer, Wehrheim, Germany). Routine staining methods of all organs were Hematoxylin-Eosin (H. and E.) and Masson's trichrome stain. The skin samples were also stained...
Table 1. Sex, age, body weight affected by pachyonychia in S. oedipus oedipus

<table>
<thead>
<tr>
<th>Necropsy no.</th>
<th>Animal no.</th>
<th>Sex</th>
<th>Age*</th>
<th>Body weight (g)</th>
<th>Claw dystrophy</th>
<th>Alopecia</th>
<th>Pigment spots</th>
<th>Melanocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>437</td>
<td>142</td>
<td>M</td>
<td>2.66 yr</td>
<td>240</td>
<td>+</td>
<td>+</td>
<td>n.r.</td>
<td>0</td>
</tr>
<tr>
<td>1044</td>
<td>437</td>
<td>F</td>
<td>2.5 yr</td>
<td>437</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>1085</td>
<td>164</td>
<td>F</td>
<td>4.75 yr</td>
<td>231</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>1218</td>
<td>18</td>
<td>F</td>
<td>adult</td>
<td>430</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>1250</td>
<td>438</td>
<td>M</td>
<td>3.3 yr</td>
<td>410</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>1353</td>
<td>788</td>
<td>M</td>
<td>3 yr</td>
<td>393</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>1371</td>
<td>902</td>
<td>F</td>
<td>2.25 yr</td>
<td>404</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
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<tr>
<td>1514</td>
<td>159</td>
<td>F</td>
<td>adult</td>
<td>510</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>1600</td>
<td>1290</td>
<td>F</td>
<td>2 yr</td>
<td>275</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>1601</td>
<td>1291</td>
<td>F</td>
<td>2 yr</td>
<td>333</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>1843</td>
<td>5272</td>
<td>F</td>
<td>9 m</td>
<td>250</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>1844</td>
<td>5271</td>
<td>M</td>
<td>9 m</td>
<td>235</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>1845</td>
<td>5273</td>
<td>F</td>
<td>9 m</td>
<td>279</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

Control animals

<table>
<thead>
<tr>
<th>Necropsy no.</th>
<th>Animal no.</th>
<th>Sex</th>
<th>Age*</th>
<th>Body weight (g)</th>
<th>Claw dystrophy</th>
<th>Alopecia</th>
<th>Pigment spots</th>
<th>Melanocytes</th>
</tr>
</thead>
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<tr>
<td>1018</td>
<td>585</td>
<td>F</td>
<td>1 y 8m</td>
<td>535</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ + +</td>
</tr>
<tr>
<td>1029</td>
<td>63</td>
<td>F</td>
<td>adult</td>
<td>353</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ + ±</td>
</tr>
<tr>
<td>1227</td>
<td>38</td>
<td>M</td>
<td>adult</td>
<td>409</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ + +</td>
</tr>
</tbody>
</table>

*yr = year; m = month.

for melanin using Fontana's and Schmorl's techniques. The resin-embedded claws were stained with toluidine blue, alcian blue, PAS, and Movat's methenamine silver technique.

**Results**

**General**

Table I summarizes the most pertinent data of the animals, such as individual numbers, sex, age, and body weight at life termination. The table also indicates the presence of alopecia and of claw pathology in the animals. Figures 1–6 construct the pedigrees of the affected animals.

**Gross pathology**

Skin. The alopecia was generalized (Fig. 7) in most cases (8 ×), but sometimes spared the long, white hairs of the cranium. If less advanced, the alopecia most prominently affected the trunk and the outsides of the anterior and posterior extremities (3 × 4). In one animal only the tail was alopecic; one early observation does not state the extent of the alopecia.

Association with the alopecia was a spotty appearance of the truncal skin due to leukoderma, contrasting sharply with pigment spots up to 1 cm in diameter. It extended and exaggerated the focal pigment spots in the pigmented skin of the extremities, that could be seen also in some adult cotton topped tamarins without any signs of skin disease.

Claws and nails. The claw pathology mentioned in Table I consisted of elongation, thickening, dorsal flexion, torsion, and corkscrew-like twisting, and greyish-yellowish to white-yellowish discoloration of one or more claws Fig. 8). The disorder principally affected all claws and the nails of the big toes, but tended to prefer symmetrically the digits 2–4 of the extremities (Fig. 9).

The elongated claws (up to several centimeters) caused difficulties in walking and climbing of the diseased animals. Shortening (cutting) was only of transitory help—within a few weeks the elongation reappeared.

**Histopathology**

Skin. In the skin samples a slight acanthosis, to some degree also proliferation and irregular arrangement of more basal cell layers, was noted. Epidermal melanotic melanocytes were markedly reduced in numbers, with focal/multifocal arrangements. The numbers of adnexal elements were grossly reduced or altogether lacking. The normally composed hair follicles were reduced to single primary hairs or altogether lacking and, with one exception, were in the telogen or catagen phase. Sometimes the follicles contained horny plucks or seemingly dystrophic hairs in the infundibulum; others were reduced to short hair germ-like buds in the epidermis. Even in the cases of entirely lost hair follicles the former presence and location of primary hairs was still indicated by evenly distributed *Mm. arrectores pilorum*.
Fig. 1. Pedigree 1.

Fig. 2. Pedigree 2.

Fig. 3. Pedigree 3.

Explanations to Figures 1–6. Numbers within the sex symbols are the animal registration numbers; those below the symbols state the age at the time of death or ( ) at present.

Parallel to the hair loss was a reduction in size and number or a total absence of holocrine sebaceous glands, and also the apocrine sweat glands were diminished as well but were never entirely lost.

Upper dermal inflammatory responses were almost always present but similar minor inflammatory dermal infiltrates of the same distribution were observed also in the control animals.

Dermal melanotic melanocytes were markedly increased in number as focal or multifocal accumulates, which possibly correspond to the grossly seen pigment spots. They were seen only rarely in the control animals.
Claws. In the grossly elongated claws the most conspicuous lesion was acanthosis of the deep epidermal layers, which was most pronounced in the area of the coronary band but also resulted in thick prickle cell layers of more than 10 cell layers in the dorsal and solar aspects of the claw. Intracellular edema and nuclear pyknosis were spread in focal distribution throughout the deep keratinocytes; epidermal melanotic melanocytes were identified only in the solar noncornified epidermal layer. The proliferated prickle cells in the upper layers commonly underwent degenerative changes ranging from single cellular keratinization or epidermal necrolysis to epidermolytic hyperkeratinization with appearance of large amorphous microvesicles filled by proteinaceous, PAS-positive materials. The slightly parakeratotic stratum corneum was quite irregular, with the appearance of longitudinal clefts in the dorsal portion especially, some being filled by cellular debris or ghost cells, others being empty. The horny layers of the solar parts of the claws showed a wavy pattern of whorl-like structures instead.

Population studies

Genetic back-tracing of the affected animals (positive phenotype) revealed their concentration in (so far) eight particular families. In two more families founded by mating of a phenotypically positive parent (homozygote?) with a phenotypically negative mate, the neonatal mortality rate of 100% prevented the expression of any phenotypes in the offspring. Expression age was at least 6 months, according to the caretakers’ reports, but the exact onset of the disease was difficult to establish. Therefore, the margin of the phenotype expression was arbitrarily set at 6 months of age in the following description.

Family 44/18 (Fig. 1)

History. Number 44 was acquired with the original colony without history and sacrificed at old age (arthrosis); phenotype: φ.

Number 18 was acquired with the original colony without history and sacrificed at more than 10 years of age (decompressed heart failure). See also family 486/25; phenotype: φ.

The reproduction record of the family is as follows: Total offspring—15; death below phenotypical age—12 (death rate 80%); phenotypical age reached—3; positive phenotype—3 (100%).
Family 66/67 (Fig. 2)

*History.* Number 66 was acquired with the original colony without history. Death occurred at more than 10 years of age (see also family 66/88); phenotype: Ø.

Number 67 was acquired with the original colony without history and sacrificed at adult age (pulmonary carcinoma). See also family 438/67; phenotype: Ø.

The reproduction record of the family is as follows: Total offspring—12; death below phenotypical age—2 (death rate 17%); phenotypical age reached—10; positive phenotype: 2 (20%).

Family 66/88 (Fig. 3)


Number 88 was an F1-generation of number 77/78 of the original colony, both parents of negative phenotype.

It is alive, on breeding loan to another colony. Phenotype is Ø.

The mating of number 88 with her own son (number 179) resulted in seven offspring, three of which died neonatally, the remaining four reaching adulthood without signs.

The reproduction record of the family is as follows: Total offspring—4; death below phenotypical age—3 (75%); phenotypical age reached—1; positive phenotype—1.

Family 195/266 (Fig. 4)

*History.* Number 195 is the brother of number 88 (see above). It is alive, phenotype—Ø.

Number 226 is an F1-generation of 74/75 of the

Fig. 9. Distribution of dystrophic claws/nails in pachyonychia of *S. oedipus.*
original colony, both parents of negative phenotype. It is alive, phenotype—∅.

The reproduction record of the family is as follows: Total offspring—17; death below phenotypical age—6 (35%); phenotypical age reached—11; positive phenotype—2 (18%).

Family 224/692 (Fig. 5)

History. Number 224 is an F1-generation of numbers 3/4 of the original colony (both parents and 15 siblings of negative phenotype). It is alive, phenotype—∅.

Number 692 is an F1-generation of numbers 62/63 of the original colony (both parents and 11 siblings of negative phenotype). It is alive, phenotype—∅.

The reproduction record of the family is as follows: Total offspring—13; death below phenotypical age—6; phenotypical age reached—7; positive phenotype—3 (43%).

Family 486/25 (Fig. 6)

History. Number 486 was acquired from the University of Bielefeld, Germany and sacrificed at 2.5 years of age (skin ulceration); phenotype—∅.

Number 25 was acquired with the original colony without history, sacrificed at more than 10 years of age (colorectal cancer); phenotype—∅.

The reproduction record of the family is as follows: Total offspring—4; death below phenotypical age—3 (75%); phenotypical age reached—1; positive phenotype—1 (100%).

Family 438/67 (Fig. 1)

History. Number 438 was the offspring of 44/18; it was sacrificed at 3 years of age (diagnostic reasons); phenotype—+.

Number 67 was discussed above in 66/67; phenotype: ∅.

The reproduction record of the family is as follows: Total offspring—2; neonatal death—2 (100%).

Family 28/18

History. Number 28 is male, acquired with the original colony without history; it is alive, phenotype—∅.

Number 18—see 224/692; phenotype—+.

The reproduction record of the family is as follows: Total offspring—2; neonatal death—2 (100%).

Discussion

Nontraumatic, noninfectious, localized, or less commonly widespread, to total alopecia of non-human primates has been related to a variety of causes ranging from protein-caloric malnutrition in wasting syndromes [2] to deficiencies in sulfated proteins [5], to zinc deficiencies [3,21,23], to stress-induced ketosteroid or glucocorticoid hyperproduction [10], to autoimmune diseases [8].

None of these pathways could explain the epidermal disease observed in the cotton-topped tamarins at the DPZ. The symmetric hyperplasia of sometimes-single claws on every extremity cannot be explained by any nutritional or metabolic influences; almost all animals were in a normal age-related weight range; and zinc supplementation or corticosteroid-treatment did not have any effect. The dystrophic-hyperplastic claws can easily be distinguished from overgrowth caused by disuse of one or more extremities by its gross appearance. Claws simply growing longer because of lack of mobility retain their dark black-brown color, are not thickened, and are pointed, whereas the dystrophic claws were greyish-yellow, thickened, often twisted, and very often blunt-ended or broken.

The familial concentration of the patients with only a small portion of the entire tamarin population being affected suggested a hereditary epidermal disease instead. Somewhat similar genodermatoses have been reported in cats as autosomal recessive feline alopecia universalis or in certain canine breeds—all without claw pathology (for detailed description see [9]).

In man a hereditary disease marked by alopecia, pigmentation defects, and nail thickening has been reported as pachyonychia congenita [1,6,9,11,22,24]. It occurs predominantly as an autosomal dominant, in rare cases as autosomal recessive [4,13] trait, expressed in several combinations of the defects. The disease in the cotton-top tamarins, reported here, is characterized by alopecia, claw (resp., nail) thickening, and in many cases by dyspigmentation particularly of the truncal skin, as resembling the human disease. Genetically it is marked by the following:

1. Familial occurrence. Out of the many (and changing) S. oedipus-families kept at the DPZ, only eight families produced phenotypically positive offspring.
2. One parent of one family (#486) has not been bred in the DPZ, but came from another, locally distant colony.
3. Affected phenotypes were expressed in both sexes with a preference of females (males: females = 1:3).
4. The parental, and, if known at all, also the grandparental generations were phenotypically negative in most families (66/67; 66/88; 195/226; 224/692, and 481/25).
5. The occurrence rate of phenotype expression in the offspring of phenotypically negative parents (only offspring of more than 6 months included) ranged from 18 to 100%, the great variation being influenced by the exceptionally high neonatal mortality rate in some families. If all affected families were combined, the occurrence rate was 12/32 = 37.5%.

6. In three families with one phenotypically positive parent (28/18; 44/18, and 438/67) the neonatal/infantile fatality rate was exceptionally high (80% and 100% respectively) with all three survivors expressing the genodermatosis already at less than 9 months of age. A similarly high neonatal death rate (75%) was observed in two affected families of phenotypically negative parents (66/88 and 486/25), again with both survivors becoming phenotypically positive at adult age. The neonatal death rate of 75–100% has to be compared to the overall neonatal/infantile mortality rate of 45–50% in S. oedipus at the DPZ and elsewhere [15]. It suggests a reduced reproductive fitness in all families of a phenotypically positive parent and in some families of phenotypically negative parents.

Taking all these facts into consideration, the familial occurring ectodermal disease in the cotton-top tamarins seems to be linked to an autosomal gen-focus. Certain points are in favor of a recessive trait such as phenotypically negative parents and grandparents and the appearance of less than 50%. Ideally it should be 25% instead of 37.5%; however, even known recessive traits of man quite commonly deviate from that ideal proportion by reaching 39% due to low offspring rate and neglecting families of heterozygotic parents without a diseased child [20]. The applicability of the Mendelian law might be further complicated in the callitrichids, the small neotropical primates that include the tamarins and marmosets, since callitrichids normally produce twins or even triplets, which are hematopoietic chimeras due to the presence of placental anastomoses. But if it is to be considered to be a recessive trait it would mean the presence of the genomic defect also in cotton-top tamarins of at least one other colony, because one father of a phenotypically positive offspring came from the outside. If, in contrast, it is considered as a dominant trait it would be one of lower penetrance, because in that case many of the heterozygotic parents would not have expressed the phenotype.

In summary, the disease seems to be an autosomal recessive rather than an autosomal dominant trait, but it remains a question that has to be solved in the future. If it really is a recessive trait, that would be a difference from the human situation where the similar disease is autosomal dominant. There are some other minor clinicopathological differences, some of which could be explained by anatomical or physiological differences between man and tamarins. Among the hallmark of the human disease, e.g., are palmar/plantar hyperkeratosis or hyperhidrosis, which so far have not been observed in the tamarin disease.

Abnormal pigmentations are common to both human and tamarin syndromes. In human pachyonychia it occurs as leukoderma (leukoplaikia) of oral mucous membranes that could not be identified in the normally pigmented [7] oral mucous membranes of the tamarins. Instead there were distinctive changes in the distribution of epidermal and dermal melanotic melanocytes, particularly at the trunk. Observations in the control animals of the present study and those by others [7] indicate that the normally heavily pigmented skin results from numerous evenly distributed epidermal melanotic melanocytes. Dermal melanotic melanocytes were only occasionally seen in ,normal, animals. In the diseased animals, on the other hand, the epidermal melanocytes were markedly diminished and focally/multifocally arranged and numerous dermal melanocytes were densely accumulated in the dermis.

The nail thickening in human pachyonychia congenita is characterized by hyperkeratosis subunguarius with abnormal keratinization of the nail bed or by longitudinal ungual lesions filled with granular tissue occurring in the keratinized substance between nail and nail bed [9,13]. Very much akin to the human disease were the unguicular lesions in the affected cotton-top tamarins. Normally, in the callitrichid claw, the terminal matrix and the deep, noncornified layers of the claw bed are very thin [24]. In the diseased animals the falcules were grossly thickened due to marked acanthosis of the claw bed associated with the appearance of longitudinal clefts in the stratum corneum of the paries unguiculae. In the solea unguiculae the thickening of the stratum corneum was associated with a wave-like or whorl-like arrangement of the horn lamellae.

The condition in the cotton-top tamarin can be compared to pachyonychia congenita of man but nevertheless is not identical to it. To our knowledge this is the first description of a genodermatosis in simian primates. Only in ruffed lemurs (Lemur variegatus), a prosimian species, a presumably recessive gene for hairlessness has been described [12]. Unfortunately, because of the unknown history of the DPZ cotton-top tamarins and the impossibility of purposely breeding homozygote families at the DPZ for management reasons so far, nothing can be said about the underlying mechanism. A genomic
damage from previous experimental or spontaneous exposure to virus genomes can not be excluded, although at least an experimental virological cause seems unlikely in case it is a recessive trait, because in one family the father came from another institute with no background in experimental virology.

References


