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INVITED ARTICLE

Human evolutionary history: Consequences for the pathogenesis of otitis media

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ABSTRACT

The pathogenesis of otitis media is multifactorial, but the role of evolution on its development has not been addressed. We posit that the high prevalence of middle-ear disease is most likely restricted to humans, in contrast to other wild species, because the associated hearing loss would have reduced the fitness of affected individuals as a result of predation. We present here the possible consequences of two human adaptations that may have resulted in ubiquitous otitis media: the interaction of bipedalism and increased brain size, and the loss of facial prognathism resulting from speech or cooking. As a consequence of our adaptation for bipedalism, the female pelvic outlet is constricted, which, in the context of a rapidly enlarging brain, results in humans being born 12 months too soon. Significantly, immature eustachian tube structure and function, in conjunction with an immature immune system, helps to explain the high incidence of otitis media in the first year of life. But the persistence of middle-ear disease beyond this stage is not explained by “immaturity.” The morphology of the palate changed with the adaptations that produced facial flattening, with concomitant effects on eustachian tube function. These changes resulted in relatively poor human physiologic tubal function in comparison to the nonhuman primate.

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Otitis media (OM), the most common diagnosis for children by health professionals, is also frequently encountered in adults. Indeed, OM is a major health care problem for which new measures of prevention and treatment are needed. There is general agreement that the etiology and pathogenesis of middle-ear (ME) disease is multifactorial, but the consequences of human evolutionary history for the presence and prevalence of OM have not been addressed. We have recently posited that OM is most likely a disease that occurs at such a high prevalence only in humans, in contrast to its infrequent expression in other wild species. We attribute low levels of OM in wild species to the associated hearing loss, which would have dramatic conse-

quences for either a predator or its prey.¹ Normal hearing is essential in the wild.

The ubiquity of OM in humans suggests to us that it is a “normal” feature of our life history. We hypothesize that design compromises resulting from two human adaptations resulted in ubiquitous ME disease: the interaction of bipedalism and our big brain, and the loss of facial prognathism. We also describe an animal model, the Cavalier King Charles Spaniel, which through artificial selection has been bred to have a short snout (reduced facial prognathism) and is reported to have a high prevalence of OM, potentially lending insight into the pathogenesis of ME disease in humans.

Bipedalism and Big Brain

One distinguishing feature of hominids when compared with our predecessors, including our nonhuman primate ancestors, is habitual bipedalism (Fig 1). Adaptations for bipedality are evident in one of our ancient ancestors, *Ardipithecus ramidus*, who lived more than four million years ago.² There is no consensus on the evolutionary advantages of either walking and running on two legs or knuckle walking, as in the great apes, over quadrupedal locomotor patterns. However, among the hypothesized advantages of bipedality are improved thermoregulation due to decreased exposure of the body to the sun, the ability to carry (including food and infants), the ability to see over the savannah for food and predators, and freeing of the hands, allowing tool- and weapon-making.

We are all familiar with the disadvantages that develop as a result of bipedality, including bad backs and joints of the lower limbs, both of which develop after reproductive age. But, an even more significant disadvantage arising from bipedality is the constriction of the pelvic outlet. The narrowing of the outlet is thought to arise as a consequence of the need for osseous support of the abdominal contents and changes that increase biomechanical efficiency in locomotion. For early hominids, these anatomical changes did not impair the delivery of newborns because their brains and bodies were small relative to their mother’s size. However,

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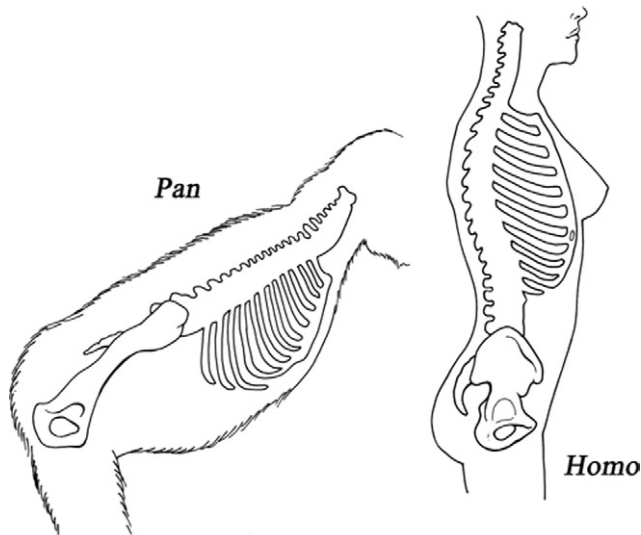


Figure 1 Line drawing comparing the locomotive posture of the chimpanzee (*Pan troglodytes*) with the human (*Homo sapiens*).

during the subsequent two million years, the hominid brain approximately doubled in size, such a large increase that the human newborn is born 12 months too early due to the constraints imposed by our big brain on passing through the relatively small pelvic outlet. This sequence of events is well known to anthropologists, as concluded by Martin,³ who stated that, based on brain development, humans should have a 21-month gestation period; nine months in the uterus and 12 months outside the womb. This is illustrated in Figure 2, which depicts the relative sizes of the female bony pelvic birth canal to the size of the brain in the chimpanzee and human.⁴ Delivery of human newborns is so tight that almost all pregnancies require birth attendants or, as in the last 2000 years, a cesarean section. We are the only species that needs assistance during parturition.

We previously described, in detail, the comparative anatomic and birthing differences between humans and our primate relatives, as well as the consequences of being “born too soon” for the ears, nose, and throat.⁵ Among these consequences is that the eustachian tube (ET) is too short and floppy during the first year of life. This structural and functional immaturity, in the context of an immature immune system, helps to explain the high incidence of acute OM in the first year of life, especially now that child daycare attendance exposes these highly susceptible babies to respiratory pathogens. A recent report from Norway finds recurrent acute OM more prevalent during the first 18 months of life in premature infants when compared with normal-term babies.⁶ This difference was attributed to gestational age differences, not weight at birth, thus, premature infants are “born way too soon.” But, being born too soon does not explain why OM remains common throughout childhood and, in some individuals, into adulthood.

Loss of Facial Prognathism (Facial Flattening)

The second relevant difference observed in modern humans, when compared with our hominid ancestors and extant nonhuman primates, is facial flattening, or the loss of facial prognathism.⁷ This is evident in Figure 3, a human-chimpanzee skull comparison that shows the reduction and repositioning of the maxillofacial complex in the human. Facial flattening, along with descent of the hyoid, contributed to shortening of the palate.⁸ We have described these evolutionary adaptations in detail elsewhere.¹ So why have we lost our facial prognathism?

Speech

What other unique adaptation did *Homo sapiens* acquire during evolution? Humans are the only species that developed speech. During our evolution, in a short 40,000 years, our larynx descended, elongating the supralaryngeal vocal tract into a two-tube configuration that enhanced speech.⁹ This adaptation narrowed the pharyngeal airway and shortened the palate, which probably aids in the production of vowels and consonants, but also has consequences for the palatal muscles (described later).

Cooking

Cooking of food may be another possible explanation for our facial flattening. As recently described by Wrangham,¹⁰ the earliest evidence of cooking by hominids dates back

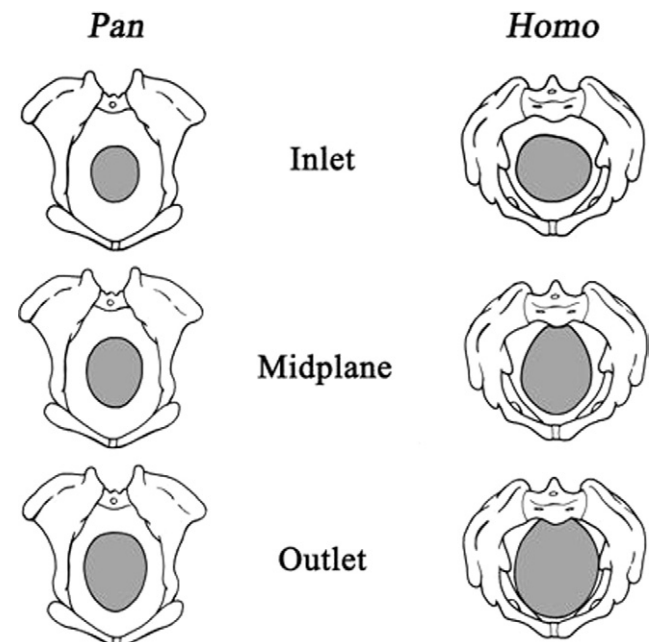


Figure 2 Line drawing comparing the pelvic inlet, midplane, and outlet with the brain size (shaded) of the chimpanzee to that of the human at birth. The brain of the newborn chimpanzee has ample room for an uncomplicated birthing, but even at nine months' gestation, the large-brained human has a tight squeeze during delivery. Adapted from Tague and Lovejoy, 1986.⁴



Figure 3 Comparison of skulls between the human (*left*) and chimpanzee (*right*) that shows the dramatic facial flattening in the human.

almost two million years to *Homo erectus*. He hypothesizes that cooking provided the necessary caloric density to meet the energy requirements of our rapidly growing brain. An ancillary effect of this change in dietary processing was an alteration in the size and shape of our teeth, a shorter maxilla and mandible, and relatively small oral cavity in comparison to other hominids. Although speculative, this is an attractive hypothesis to explain both the increase in human neonatal body and brain size and the loss of facial prognathism.¹¹

Change in Palate Morphology Related to Eustachian Tube Function

Whichever causal mechanism is responsible for our facial flattening, it changes palatal anatomy, including the muscles of the palate involved in eustachian tube function (ETF), muscle tensor veli palatini (mTVP), and muscle levator veli palatini (mLVP). They became less effective physiologically than in the nonhuman primate (*Macaca mullata*).¹ When we compared the ETF of monkeys and humans, monkey dilatory (opening) tubal function was consistently superior.¹² Relatively speaking, humans have poor tubal function. This becomes evident during activities that impose nonphysiologic stresses on the ET, such as flying in airplanes and scuba diving, during which equalizing ME negative pressure becomes problematic. By contrast, even the application of sudden large negative ME pressures in the monkey were easily equilibrated with a single swallow.

The physiologically inferior function of the human ET compared with that of the monkey is most likely due to differences in the anatomy of the paratubal muscles. **Figure 4** is a photograph of a cross-section of the ET showing a relatively slim mTVP attached to the lateral lamina of the tubal cartilage and the relatively large belly of the mLVP, a rounded mass that abuts the inferior portion of the tubal lumen. Even though the rhesus monkey's genome is similar to ours, and although we have employed them in our laboratory as a model for humans in studies involving the physiology and pathophysiology of the ET and the pathogenesis of OM, the paratubal muscles of the rhesus are *not* identical to humans. Comparison of the anatomy of these

two muscles between the monkey and the human reveals two major differences: 1) in the monkey, the mTVP has more bulk and attaches to the entire length of the cartilag-

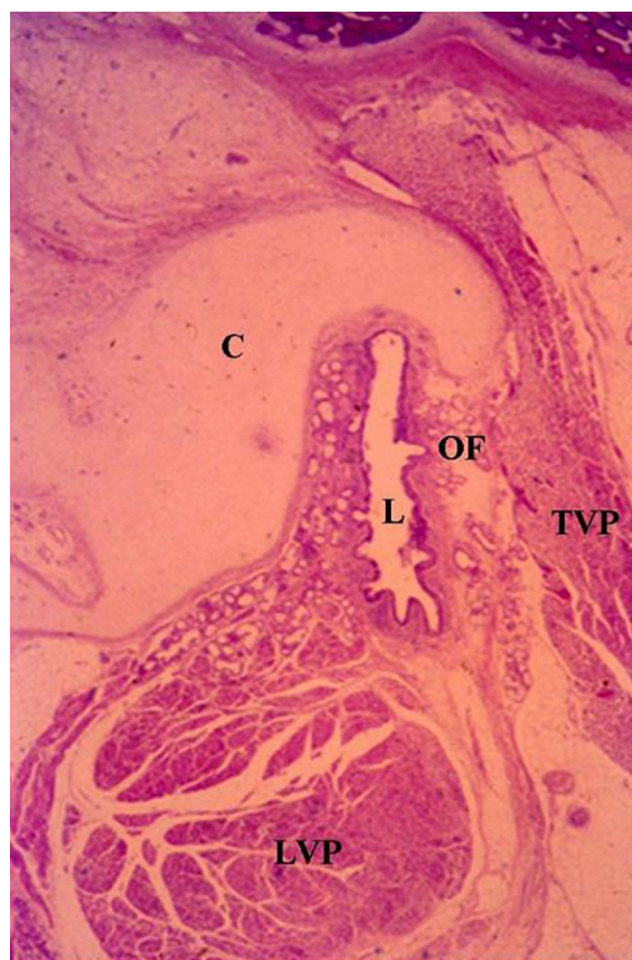


Figure 4 Cross-section through the mid-cartilaginous portion of a left human eustachian tube. Note the robust rounded belly of the levator veli palatini muscle abutting the inferior portion of the tubal lumen, and the rather thin slip of the attachment of the tensor veli palatini muscle to the lateral lamina of the tube. *C*, tubal cartilage; *L*, tubal lumen; *LVP*, levator veli palatini muscle; *OF*, Osmann's fat pad; *TVP*, tensor veli palatini muscle. (Courtesy: I. Sando, MD.)

inous ET, whereas in the human this muscle is not as robust and attaches to only the mid-portion of the ET; and 2) the belly of the mLVP is not as prominent and does not impinge on the inferior portion of the tubal lumen in the monkey in contrast to the human condition (Fig 4).¹³

Eustachian Tube Muscles Related to Pathogenesis of Human Middle-Ear Disease

As opposed to the extraordinarily high incidence of OM in humans, particularly in childhood, we have almost never observed spontaneous ME disease in the outbred animals (e.g., ferrets and monkeys) we have had in our laboratory over more than 30 years. Is this remarkable difference in the rate of OM related to the comparatively poor ETF a consequence of differences in paratubal muscular anatomy in *Homo sapiens* as compared with the monkey? Experiments with the monkey in our laboratory undergirded our understanding of the pathogenesis of ME disease in the human.¹⁴ We have successfully created OM in this animal model by inactivating the mTVP by either severing the tendon at the hamulus of the pterygoid bone or by injecting botulinum toxin into its belly. Since the mTVP is the only muscle that opens (dilates) the tubal lumen during swallowing, ME effusion develops when it is rendered nonfunctional. We concluded that a healthy mTVP is important in the prevention of OM. Hypothetically, since the monkey's mTVP is larger and has a longer attachment to the tube, producing excellent tubal function, impairment of ETF due to inflammation should not result in OM. Humans, on the other hand, with comparatively poor tubal function, are susceptible to inflammatory conditions that degrade ETF, resulting in OM. Indeed, Buchman and colleagues¹⁵ reported that some adult volunteers who had nasal challenge with virus developed ME disease. Why viral infection affected some subjects and not others may be explained by the results of a later study in which adult volunteers who had signs of ET dysfunction prior to a viral challenge were the ones who developed more severe dysfunction and ME under-pressures. Subjects with good tubal function before the challenge did not develop OM.¹⁶

Thus, the relatively inefficient human mTVP is a viable candidate for the pathogenesis of ME disease in some individuals, but what role might the mLVP play in OM? We have reported that older children and adults with chronic OM with effusion had ET dysfunction characterized by *constriction* of the ET, as opposed to dilation, during swallowing on the forced response test.¹⁷ This observation in the context of electrical stimulation of the monkey paratubal muscles¹⁸ suggests that the constriction is most likely due to contraction of the mLVP, which collapses the tubal lumen during attempts to dilate the ET. This hypothesis is currently under investigation in our laboratory.

The possible role that mLVP plays in tubal constriction is illuminated further by our studies of children with cleft palate. The infant with an unrepaired cleft palate is an *in vivo* model of chronic ME disease, which has been shown to be a functional, as opposed to an anatomic,

obstruction of the ET.¹⁹ Constriction of the tube has been identified in these babies.²⁰ Following surgical clefting of the monkey palate, OM with effusion developed.²¹ ET function tests revealed constriction of the tubal lumen that we now attribute to a dysfunction of the mLVP. Hypothetically, then, in an effort to prevent OM in these babies, surgical repair of the palate should focus on the mLVP as well as correcting their velopharyngeal insufficiency and speech defect.

Canine Model of Otitis Media and Its Implications for Human Disease

Among veterinarians, chronic ME effusion (termed *primary secretory otitis media*) is a well-known disease in the Cavalier King Charles Spaniel.²² It has been reported to be present in up to 40 percent of these animals. The effusion is mucoid and fills the entire ME. Diagnosis is made by operating microscopic examination, computed tomography scanning, or magnetic resonance imaging (MRI), and has been confirmed at the time of myringotomy. Myringotomy and tympanostomy tube placement has been recommended for treatment.²³ This breed has been artificially selected to have a shortened front-to-back diameter of the skull, a shape termed *brachycephaly*, which arises due to premature fusion of the coronal sutures. The term *neotenus* (retention of juvenile characteristics into adulthood) is also appropriate for these breeds.²⁴ The Cavalier snores habitually like other brachycephalic dogs, including the English Bulldog, a breed that has been reported to be the only animal known to develop obstructive sleep apnea. The snoring is undoubtedly secondary to its constricted pharynx, a consequence of the shortening of the snout. As reported by Davidson and colleagues,²⁵ we are also prone to obstructive sleep apnea due to our reduced pharyngeal airway. Figure 5 compares the head shape of a Cavalier King Charles Spaniel, with its extremely short face, to that of a Golden Retriever, which has a classic prognathic snout.

The Cavalier King Charles Spaniel is an animal model of chronic OM with effusion. It has been “artificially selected” (Charles Darwin's term) for its short snout and globular head, but an unintended consequence of breeding for this characteristic is the propensity for chronic OM with effusion. In a recently reported study using MRI, veterinarians from England found that not only did the Cavalier have OM (54%), but another brachycephalic breed, the Boxer, also had ME disease (32%), which was not present in Cocker Spaniels, a mesaticephalic breed. The investigators suggested that the reduced nasopharyngeal space in the Cavalier and Boxers, when compared with the Cocker Spaniel, predisposed them to OM.²⁶ It might be that one or both of the paratubal muscles is dysfunctional due to the abnormal palatal anatomy in these breeds and is the cause of their OM. The underlying pathogenesis of the Cavalier's ME disease is currently under investigation in our laboratory. Analogously, one



Figure 5 Photographs of the head of a Cavalier King Charles Spaniel (*left*) and a Golden Retriever (*right*) showing the Cavalier with an extremely short snout compared to the Golden Retriever. (With permission from Lynette Cole, DVM.)

could speculate that with the loss of their prognathic face, humans became susceptible to OM, an unintended consequence of “natural selection” for another adaptation (again, Darwin’s term), as described above.

Other Factors

We have proposed that the consequences of evolution have a role in the pathogenesis of OM in humans. But the phenomenal incidence of OM today cannot be explained solely by design compromises or the negative consequences of adaptation.²⁷ Other factors, such as heredity and immune deficiency, as well as those derived from our existence in novel environments (those we are not adapted to) such as a decrease in breastfeeding, smoking in the household, use of pacifiers and, very importantly, child daycare attendance are well known to increase the risk of ME disease.

Summary and Conclusions

Our hypothesis is that OM is primarily a human condition and that design compromises during our evolution predispose us to developing it. We have presented two human evolutionary adaptations that could produce alterations of the structure and function of the ET and contribute to the unusual prevalence of this disease: being born too soon due to the development of a large fetal brain in the context of bipedalism, and the loss of facial prognathism due to speech or cooking, when compared with our ancestors. To reduce the incidence of OM, we should pinpoint possible anatomic differences (such as the paratubal muscles) in humans as compared to other species (e.g., the monkey) that do not have ME disease, and consider them as a target for correction.

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Author Contributions

Charles D. Bluestone, co-author; J. Douglas Swarts, co-author.

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