3. 性差

高齢者において、部分容積効果補正後の脳血流に性差が認められるというLiらの報告によると、領域として、女性は、左下前頭回、両側の中側頭回、左上側頭回で、男性は左上前頭回、右上頭頂小葉、右中心後回が指摘されている[8]。しかし、血流分布の性差は、報告によって方法や結果が必ずしも一致しておらず、さらなる検討が必要であろう。

4. 脳血流を修飾する要素(「健常」をどう定義するか?)

高齢者における「健常」をどのように定義づけるかは、重要な課題である。

特に問題となるのは、虚血性変化である。高齢者は血管性すなわち虚血性の病態を背景にもっている可能性が若年者に比べて高い。症状がないことが必ずしも健常を意味しない。微小血管の変化による虚血は存在したとしても、従来の日常臨床における脳核医学検査では必ずしも評価しきれていなかった。しかし、統計学的画像解析は、そういった変化も捉える可能性がある。

白質病変やラクナ病変が存在する場合、脳血流、灰白質体積が減少する傾向にある[9,10]。したがって、健常者でも、白質病変、潜在する虚血性変化に応じて、脳血流/糖代謝が減少する可能性がある。

ApoE e4遺伝子は、アルツハイマー病(Alzheimer's disease:AD)のリスクファクターである。同遺伝子のキャリアは、ADを発症する以前、さらに若年者の段階からアルツハイマー病類似の脳血流低下パターンを示す。この点に関しては、ADの項でも再びふれる。

また、ADの特徴とされる後部帯状回の糖代謝低下は、50歳以上の健常者の約5%で認められることが知られている。このなかにADの病態をもつものが含まれることが十分考えられるが、変性性認知症の病態をもたない健常の加齢性変化をみている可能性もある。

5. 神経伝達の加齢性変化

脳血流/糖代謝の健常加齢性変化の要因として、どのような神経基盤の変化が加齢のなかで起きているか、神経伝達の観点からふれておきたい。

ドーパミンD2受容体と脳糖代謝の関係をVolkowらが検討している[11]。それによると、線条体のD2受容体結合能は、年齢に相関して低下し、脳糖代謝とD2受容体結合能が正の相関を示す領域は、前部帯状回、前頭葉皮質(前頭前野、一次運動野、眼窩前頭皮質)、側頭連合野、尾状核である。このようなドーパミン機能障害が、高齢者における運動機能障害(dyskinesis、rigidity)の基調をなすとともに、高齢者に認められる認知機能の低下の潜在的原因となっている可能性がある。また、健常高齢者に認められる実行機能(executive function)や反応抑制(response inhibition)のような前頭葉機能に関係したものもドーパミン機能低下が原因であると考えることができる[12]。

Goldbergらは、健常加齢におけるセロトニンと糖代謝の関係を、SSRI(serotonin reuptake inhibitor)の投与によって生じる糖代謝変化率を測定することで、検討している[13]。それによると、SSRI負荷による糖代謝変化率と加齢が正の相関を示したのは、右楔前部、右傍中心小葉、左中側頭回など後方域が多く、負の相関を示したのは、左前部帯状回、右の下および中前頭回など脳の前方域が多い。これらについては、加齢性のセロトニン神経支配に対する異なる補償過程があるのではないかと推論している。

神経疾患

1. アルツハイマー病

ADは、老年期で最も患者数の多い変性性認知症である。記銘力低下で発症することが多く、学習障害、見当識障害、感情の動揺も認められる。ADの臨床診断は、NINCDS-ADRDA[14]などの診断基準に基づいて行われる。核医学画像は診断基準に含まれない。

ADの脳血流SPECT、脳糖代謝PETの典型像は、頭頂側頭連合野、後部帯状回~楔前部での血流あるいは糖代謝の低下である。後頭葉、一次運動・体制感覚野付近、基底核、視床の糖代謝は保たれる(図2)。前頭葉連合野も低下する場合が多い。高齢発症のADでは、糖代謝低下が全体に小さい傾向にあり、後部帯状回~楔前部での低下がみられないものもある。その一方で、辺縁系や内側前頭葉での低下が認められる傾向がある[15]。

後部帯状回~楔前部の正常糖代謝は、脳のなかで相対的に高く、断層像上でその軽度低下を視覚的に評価することは、必ずしも容易ではない。SPM(statistical parametric mapping)[16]や3D-SSP(three-dimensional stereotactic surface projection)[17]を用いた統計学的画像解析により画素ごとに健常対照群と比較して得た統計画像

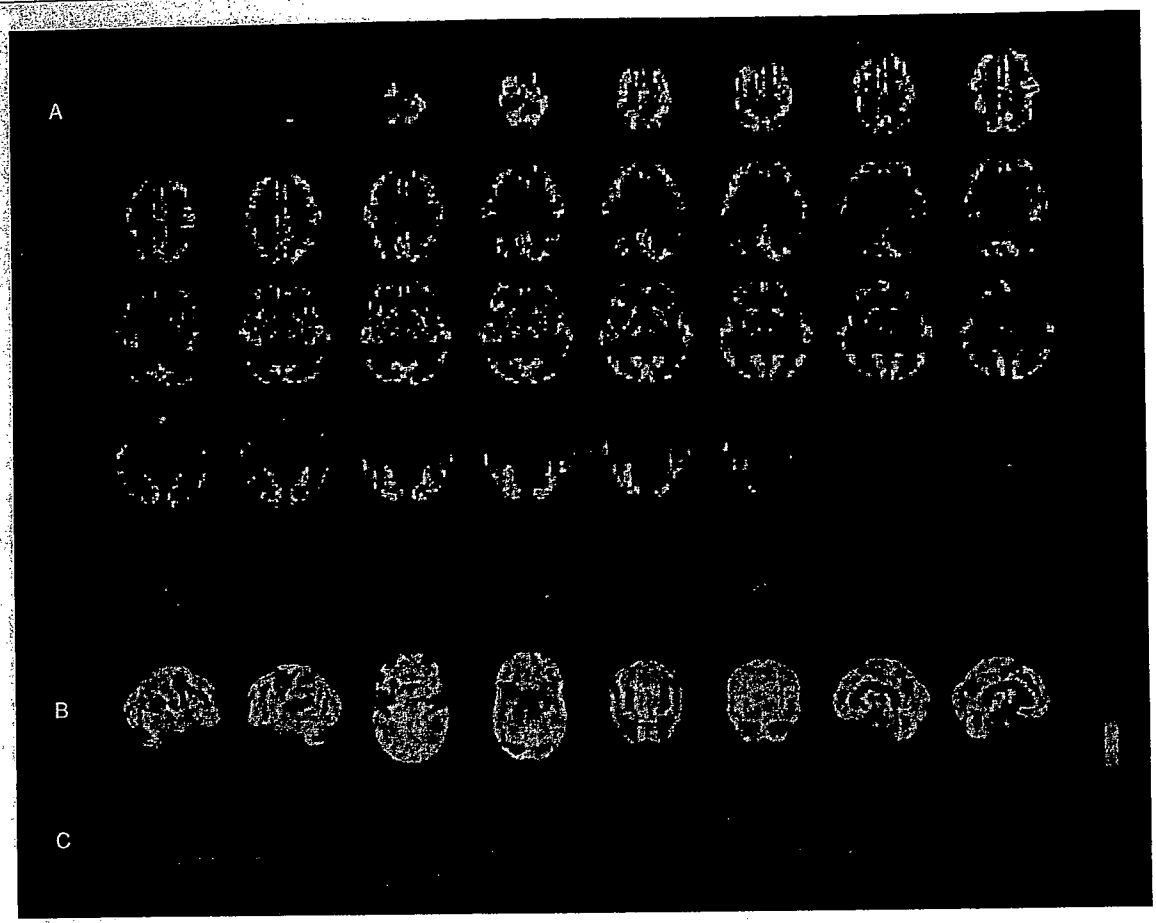

図2　AD患者の脳糖代謝PET
A　断層像
B　3D-SSP脳表投影像
C　3D-SSP Zスコア画像
頭頂側頭連合野，後部帯状回～楔前部，前頭前野での糖代謝が認められる．低下の程度は小さいが，低下域の分布は典型的である．

(Zスコア画像やT値画像)を参照することが、評価の助けになる。

2. 塩酸ドネペジルによるAD治療

塩酸ドネペジル治療は短期的には、前頭葉、頭頂葉、側頭葉の脳血流/糖代謝を上昇させる。しかし、長期的にみると治療開始前のレベルまで戻ってしまう[18]。

また、塩酸ドネペジルへの反応性は、患者によってまちまちである。治療開始前の時点で、治療反応群は、治療非反応群に比べて外側および内側前頭葉で血流が低下している[19]。また、治療に反応してMMSE(mini mental state examination)スコアが安定した群(stabilized)と治療に反応せずMMSEスコアが低下した群(nonstabilized)を比較した検討では、治療開始時点では、両群の間に差はなかったが、約1年後の時点で、nonstabilizedは、stabilizedに比べて外側および内側前頭葉、辺縁系、下外側側頭葉、帯状回でより血流が低下していた[20, 21]。治療開始時点での外側および内側前頭葉などで認められた血流増加は、stabilizedの方がより強く広範であった[21]。これらの結果は、脳血流SPECTが塩酸ドネペジルの治療効果を予測できる可能性を示している。

3. 軽度認知障害からADへの進展予測

軽度認知障害(mild cognitive impairment：MCI)は、健常(高齢者)と認知症の境界領域を表す認知機能の状態

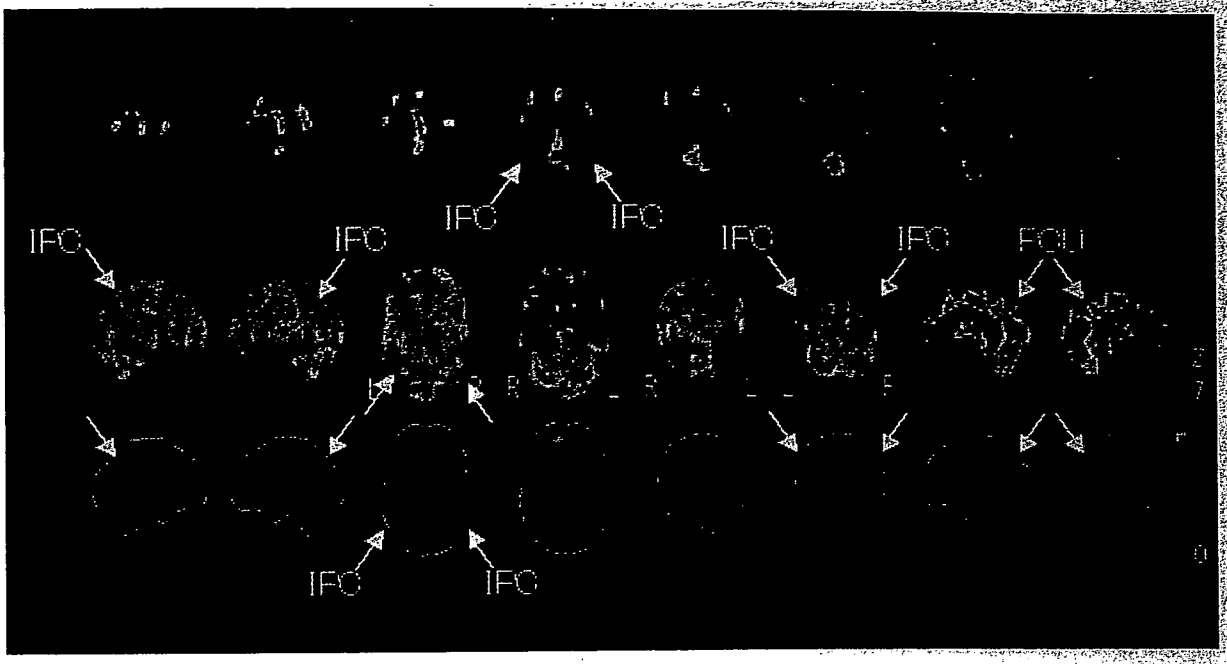

図3 MCI(AD converter)の[I-123]IMP SPECT脳血流像
上段から下段へ，断層像，3D-SSP投影像，3D-SSP Zスコア画像．MCI時点で，下部頭頂葉(IPC)，楔前部(PCU)に血流低下が認められ，アルツハイマー病の病態が存在することが疑われる．

の概念として、1999年にPetersen[22]が提唱した。MCI自体は不均一な群であるが、このなかにはADに移行する患者が高率に含まれる。4年にわたる追跡研究では、健忘を示すamnestic MCIと診断された群は、1年あたり約12％ずつADへ移行する[22]。ADへ移行するMCI(converter)においては、ADの神経病理学的変化を反映した神経活動の低下が生じていると考えられている。ADへの移行を予測する代理マーカーが何かを確定する研究が、脳血流SPECT、脳糖代謝PET、MRIを用いて行われてきた。converterとnon-converterを分ける部位として、第一に挙げるべきは下部頭頂葉ないし側頭頭頂葉 であることは各報告でおおむね共通している[23~25]。後部帯状回に関しては、converterとnon-converterを分けるpredictorであるという結果[24]と、後部帯状回より楔前部の方が重要であるとする報告[26]に分かれている。また、付随的な部位として、前頭前野、海馬、嗅内皮質が挙げられている(図3)。

Mosconi ら[27]によると、MCI患者でもApoE e4遺伝子キャリアは、e4非キャリアと比較すると、側頭頭頂葉、後部帯状回でより強い糖代謝低下が認められたという。ApoE e4遺伝子のキャリアは、症状がない段階[28]、さらには若年者の段階[29]から、脳糖代謝が後部帯状回～楔前部、頭頂側頭連合野で低下しており、AD的安静時神経活動のパターンを示すことが知られている。

アミロイドβ蛋白のイメージング用トレーサーの臨床研究も多数行われている。現在最も有力なアミロイドイメージングトレーサーは、PIB(Pittsburgh Compound B)[30]である。PIBは、ADとDLB(後述)を鑑別することはできないが、ADとFTD(後述)などの認知症を鑑別することができる。PIBの脳内集積は、MCI段階ではすでに飽和しており、MCI段階でのconverterの予測ができるだけでなく、MCIより前の段階でのAD発症を予測できることが期待されている[31]。

4. レヴィ小体型認知症

レヴィ小体型認知症(dementia with Lewy bodies DLB)は、ADに次いで頻度が高いと考えられている変性性認知症である。認知機能の変動、パーキンソニズム、幻視を症候の特徴とする。その診断基準は、2003年の第3国際ワークショップで改訂版が作成された[32]。

脳血流/糖代謝画像の特徴は、一次視覚野(鳥距領域)を含む後頭葉における血流/糖代謝の低下である。ADと同様に、後部帯状回～楔前部、頭頂側頭連合野で糖代謝が認められることも多い。他方、一次運動感覚野、線条

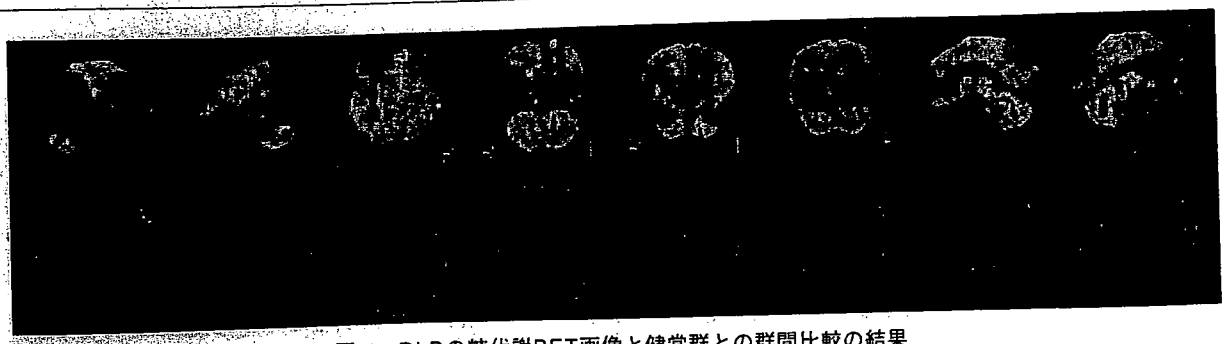

図4　DLBの糖代謝PET画像と健常群との群間比較の結果
上段はDLB群の平均脳糖代謝の3D-SSP投影像，下段は3D-SSP Zスコア画像(DLB群が健常群に比して低下している領域)．頭頂側頭連合野，楔前部～後部帯状回，前頭葉連合野に加えて，一次視覚野を含む後頭葉で糖代謝が低下している．

体、視床での糖代謝低下は認められない(図4)。

DLBでは黒質線条体系ドーパミン作動性ニューロンが変性しており、[F-18]FDOPA(fluoro-L-dopa)PET検査が、診断に役立つと考えられている[33]。また、[I-123]MIBG(metaiodobenzylguanidine)心筋シンチ検査も鑑別に有用である[34]。

脳血流/糖代謝画像での鑑別診断上の問題点は、後頭葉の所見が、DLBをADから鑑別するうえで非常に有力な指標であるが、完全ではないことである[35]。また、初期段階では後頭葉の糖代謝低下が認められず、時間経過のなかで顕在化した症例が報告されている。神経病理学的には、DLB病変とAD病変が同時に認められることがある。アミロイドイメージングトレーサーであるPIBでは、ADとDLBは鑑別できない[32]。

5. 前頭側頭型認知症(前頭側頭葉変性症)

前頭側頭型認知症(frontotemporal dementia：FTD)は、前頭葉、側頭葉に、その主たる変性を示す非アルツハイマー型の変性性認知症を包括した概念である。その最新のものが、前頭側頭葉変性症(frontotemporal lobar degeneration：FTLD)という概念である[36]。FTLDは、図5のように構成される。診断基準では、FTLDを、3つのサブグループ[frontotemporal dementia (FTD)、semantic dementia(SD)、progressive non-fluent aphasia (PA)]に分ける。FTDは、FLD(frontal lobe degeneration) type、Pick type、MND(motor neuron disease)typeの3病態を含む。FTDのうち、Pick typeとFLD typeは、最も一般的なタイプで、社会的対人関係の障害、感情の鈍化、病識の欠如といった行動や人格の変化が特徴的である。PickとFLD typeは臨床症候的には区別が困難なことが多い。

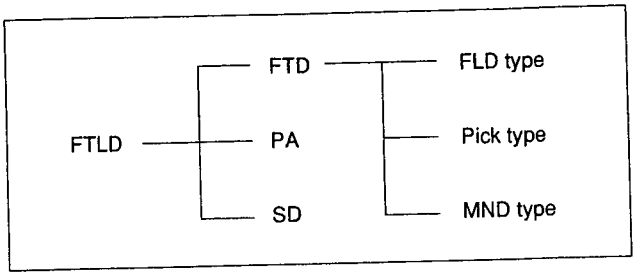

図5　FTLDの疾患概念(Neurology 1998)
FTLD：frontotemporal lobar degeneration，FTD：frontotemporal dementia，PA：progressive non-fluent aphasia，SD：semantic dementia，FLD：frontal lobe degeneration，MND：motor neuron disease

典型的なPick typeは、前頭葉に特徴的な萎縮、脳血流低下を示す。FLD typeを含めて、脳血流/糖代謝の低下は多様で、前頭葉と側頭葉(特に前部)、海馬、線条体で示し、さらに一次運動感覚野や小脳半球を含むこともある[37、38]。症状と低下部位との関連があるとされており、無気力が目立つ群と脱抑制が目立つ群で、主たる低下部位が異なる[39]。なお、SDも、側頭葉先端部に萎縮、脳血流/糖代謝の低下を示し、比較的特徴的である。

FTDでは後部帯状回～楔前部、頭頂葉連合野に糖代謝低下を生じることもあるので、これら領域の脳糖代謝低下の有無をもって、単純にADとFTDを鑑別することはできない。また、低下パターンだけなら脳血管障害性変化や進行性核上性麻痺(progressive supranuclear palsy：

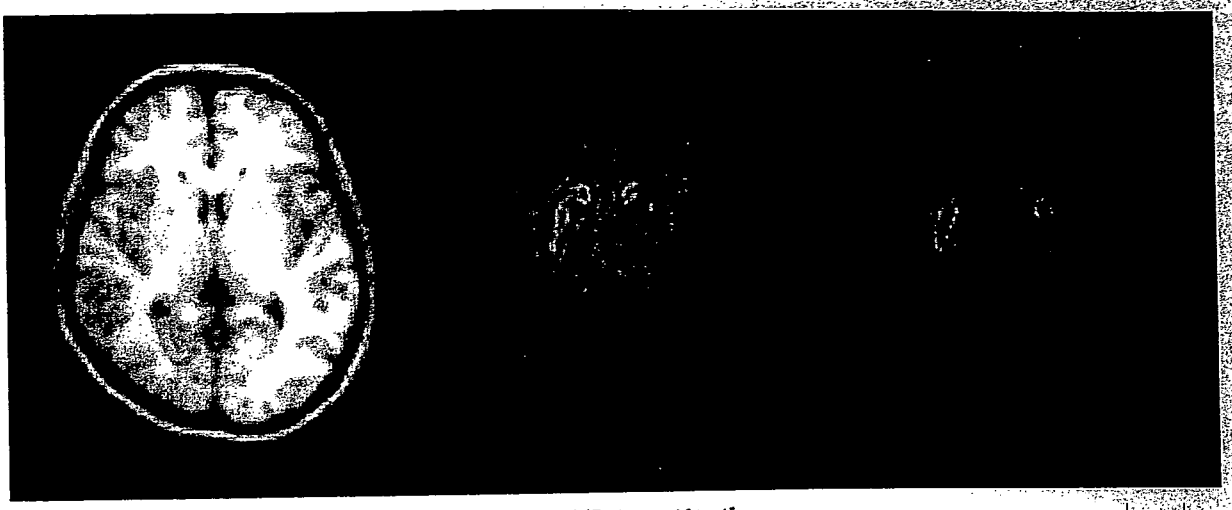

図6 PDのドーパミン神経イメージング
A 同一断面のMRI T1強調画像
B [F-18]FDOPA PET画像
C [C-11]raclopride PET画像
FDOPAは前シナプスに集積し，raclopride は後シナプスのD2受容体に結合する．FDOPAは，左右の被殻特に左優位かつ後部優位に集積が低下している．racloprideの集積低下は認められない．

PSP)との鑑別が問題となる可能性もある。

6. パーキンソン病

PDは高齢者に多い神経変性疾患で、黒質線条体系のドーパミン作動性ニューロンの変性に起因するさまざまな運動障害が主症状である。ドーパミン前シナプス機能は低下するが、晩期を除いて後シナプス機能は保たれる。したがって、前シナプスの酵素活性をみる[F-18]FDOPA、前シナプスのドーパミントランスポーターに結合する[F-18]CFT、[I-123]β-CITといったトレーサーで前シナプスを、ドーパミン後シナプスに存在するD2受容体に結合する[C-11]racloprideで後シナプスを、それぞれ分けることで、パーキンソン病の病態をイメージングすることができる(図6)。

脳血流/糖代謝に特に特徴的な変化パターンは存在しない。ただし、症例によっては、線条体の糖代謝が大脳皮質に比べて相対的に高い、後頭葉での糖代謝が低い、一次運動野の糖代謝が相対的に高い[40]といった傾向を示すことがある。後頭頭頂葉の血流は視覚認知機能と相関する[41]。また、visual hallucinationを示す群では左上前頭回で糖代謝が高く[42]、自律神経障害の強い群では後頭葉～頭頂葉で糖代謝が低い[43]という傾向がある。

パーキンソン病では、運動障害の他に認知機能の低下をしばしば示す。また認知症を示すこと(Parkinson's disease with dementia：PDD)も珍しくない。PDDとDLBは、細かくみると症候的に異なる特徴を示す部分もあるが、レヴィ病変を示す疾患(Lewy body disease)として一つのスペクトラムに含まれると考えられている。

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Spontaneous smile and spontaneous laugh: An intensive longitudinal case study

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Abstract

One male infant was observed from the day of his birth to the end of the 6th month. Total observation days were 171 days, and total observation time was 329 h 25 min and 35 s. Five hundred and sixty-five spontaneous smiles and 15 spontaneous laughs (smiles accompanied by vocal sounds) were observed. Developmental psychologists have thought that spontaneous smiles integrate at about 3 months, but spontaneous smiles were recorded even in the 6th month. The percentage of bilateral smiles increased from the 2nd month. This is the first intensive longitudinal study on spontaneous smiles and spontaneous laughs.

Keywords: A newborn infant; Spontaneous smiles; Spontaneous laughs; An intensive longitudinal case study

In a study of observations of newborns, Wolff (1959) noted: "Spontaneous smiling (defined as a slow, gentle, sideward and upward pull of the mouth, without rhythmical mouthing movements or contraction of other facial muscles) was observed ... during irregular sleep, drowsiness, and alert inactivity, but never during regular sleep, alert activity, or between bursts of crying (p. 115)". And Wolff (1987) wrote that "Endogenous or spontaneous smiles in sleep ... have sometimes been referred to as precursors of social smiling (p. 39)". Spontaneous smiles might be one of the roots of our positive emotions.

Certainly several researchers have observed spontaneous smiles (Emde, McCartney, & Harmon, 1971; Freedman, 1965, 1974; Gewirtz, 1965), but there has been little systematic research. We know two exceptions: Shimada (1969) observed 84 infants from 1 to 7 weeks cross-sectionally (at one point in time). He found that spontaneous smiles tend to be more frequent at first, and, with time, their frequency decreases while their duration increases. Messinger et al. (2002) studied Duchenne smiles (involving cheek raising) and non-Duchenne smiles (absence of cheek raising) in 25 neonates (mean age = 55 h). One-half of the neonates showed bilateral Duchenne smiles.

Kawakami et al. (2006) presented the fundamental data of spontaneous smiles and spontaneous laughs (smiles accompanied by vocal sounds). They observed 10 newborn infants cross-sectionally and 6 infants longitudinally. Uni-

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lateral spontaneous smiles were more common than bilateral smiles in neonates, but by 2 months, 80% of spontaneous smiles were bilateral. The mean duration of spontaneous laughs was longer than that of spontaneous smiles, and all spontaneous laughs were bilateral.

Both Messinger et al. (2002) and Kawakami et al. (2006) claim the necessity of longitudinal studies on spontaneous smiles to shed light on the genesis of affective expressions. This paper is the first intensive longitudinal research on spontaneous smiles and laughs. This preliminary study will explore more elaborate longitudinal research design for studying these behaviors.

Kawakami et al. (2006) concluded that "spontaneous smile" and "spontaneous laugh" might be different behaviors from the beginning. Recently, Waller and Dunber (2005) examined smiling-like display and laughing-like display in chimpanzees. To consider more detail on differences between spontaneous smiles and laughs in humans, we want to add longitudinal data.

The purposes of this study were (1) to present intensive longitudinal data of spontaneous smiles and spontaneous laughs, and (2) to further investigate the differences/similarities of spontaneous smiles and spontaneous laughs.

1. Method

1.1. Participant

One Japanese boy was observed from the day of his birth to the end of the 6th month. He had no recognized medical problems, and had experienced normal delivery. His birth weight was 2610 g. The Apgar score at the delivery was 9, and 5 min later it was 10. The gestational age was 38 weeks 6 days.

1.2. Procedure

It is difficult for researchers to record spontaneous smiles and laughs systematically because they occur unpredictably in association with irregular sleep. As adopted by Kawakami et al. (2006) and Takai (2005), we asked the mother to record spontaneous smiles and laughs by herself. The recording conditions were (1) record baby's face from near position, (2) at sleeping time, (3) on a bed if possible, (4) in silent circumstances, (5) using a tripod if possible.

Total observation days were 171 days within 181 days (6 months), and total observation time was 329 h 25 min and 35 s, 7.6% of that period of his life time. The recording strategy of the mother was "(1) all sleeping time in their home, (2) in silent circumstances, (3) when she was awake".

According to Japanese regulations, we are not required to obtain approval for this work from a Research Ethics Committee.

1.3. Definition of "spontaneous smile"

Oster (1978) used three criteria to code an infant's smile: (1) the action had to appear subjectively smile-like when viewed at normal speed; (2) there had to be more than a trace of AU12 [Action Unit in the Facial Action Coding System (FACS), Ekman & Friesen, 1978]; and (3) the AU12 component of the smile had to be visible for at least 1 s. AU12 (lip corner raising) is recognized as the basis of all smiles by other researchers (Messinger et al., 2002). Also, "lip corner raising" is an important criterion in other facial coding systems [e.g., Code 52 in The Maximally Discriminative Facial Movement Coding System (MAX), Izard, 1983].

We used strict criteria for identifying spontaneous smiles as follows: (1) lip corner raising (AU12 in FACS and Code 52 in MAX); (2) during irregular sleep, drowsiness; (3) without known external or systematically demonstrable internal causes (Wolff, 1961); (4) continuing more than 1 s; (5) smiles continued within 1/6 s are combined; (6) smiles with vocal sounds are defined as spontaneous laughs. The second criterion was used because we cannot discriminate between spontaneous and elicited smiles during an alert inactivity state.

First, we checked all tapes recorded by the mother. Second, the onset and offset of smiles and laughs were determined as follows. Our digital video camera recorder had a button to move a video sequentially by 1/30 s. When we found a smile or laugh, we moved the video back sequentially to the onset frame (immediately prior to which there were no facial movements). And from the onset, we moved the video forward sequentially to the offset (immediately following which there were no facial movements).

1.4. Coding

Two coders independently identified spontaneous smiles and laughs using the Digital Video Camera Recorder (SONY DCR-PC110). Only spontaneous smiles and laughs identified by both coders were included in the subsequent analysis. The percentage of intercoder agreement was 91.67%. Correlation of the event durations recorded by the two coders was $r = .79$ ($p < .01$).

2. Results

2.1. Spontaneous smiles

From the 9th day (no spontaneous smile was recorded until the 9th day) to 181-day-old, 565 spontaneous smiles were observed. The durations of spontaneous smiles were determined by averaging the durations recorded by the two coders. The mean duration was 2.57 s (S.D. = 1.28).

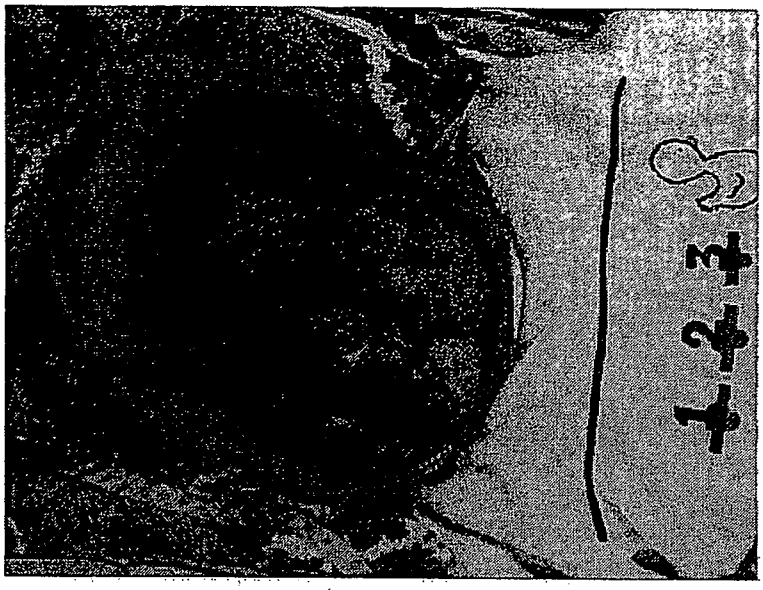
The second column of Table 1 shows the means of durations of spontaneous smiles per week. We can observe spontaneous smiles as late as 6 months of age. The fourth column shows the frequencies of spontaneous smile. By the methods adopted by this study, the comparisons of frequencies are not valuable.

At ages 4–6 months, the baby sometimes slept prone. Sixty-three spontaneous smiles were observed in this position. It is very difficult to determine the lateralities of smiles in these cases. And two spontaneous smiles were observed when he was held by the mother. Five hundred spontaneous smiles were analyzed and the lateralities noted.

Three hundred and fifty-eight were bilateral (see Fig. 1A), and 142 were unilateral. The percentage of bilateral smiles among all smiles increases from the 2nd month as shown in Fig. 2. The number of unilateral spontaneous smiles on the right side of his face (see Fig. 1B) were the same as the number on the left side (see Fig. 1C; 71, respectively). When lying on one side, unilateral spontaneous smiles were more frequently observed on the side of the face away from the surface of the bed [top side: 112, bottom side: 7; χ^2 (1) = 92.6, $p < .01$].

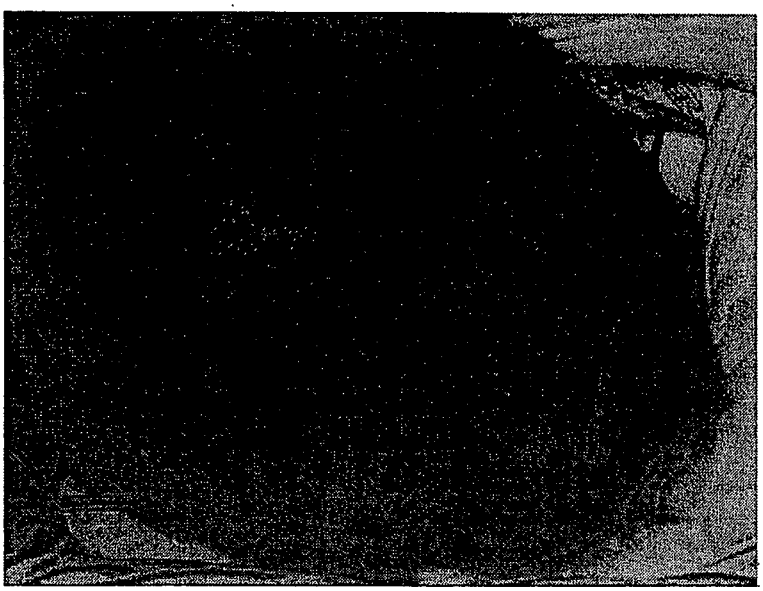
Table 1
Development of spontaneous smile

Weeks	*M* duration (s)	S.D.	Frequencies
2	2.64	1.09	21
3	2.96	1.78	19
4	2.72	.9	18
5	2.09	.77	11
6	2.48	1.4	16
7	1.79	.44	8
8	1.83	.32	4
9	2.43	1.39	14
10	2.38	.61	10
11	2.05	.89	44
12	2.66	1.18	47
13	2.43	.96	19
14	2.41	1.7	16
15	2.48	1.14	36
16	2.59	1.13	18
17	2.78	1.4	27
18	3.01	1.43	18
19	2.72	1.64	36
20	2.27	1.03	56
21	2.93	1.59	28
22	2.75	1.07	18
23	3.03	1.66	18
24	2.37	1.05	31
25	3.1	2.1	8
26	3.01	1.44	24



A (76 days-old)

B (79 days-old)



C (87 days-old)

Fig. 1. (A–C) Bilaretal and unilateral spontaneous smiles.

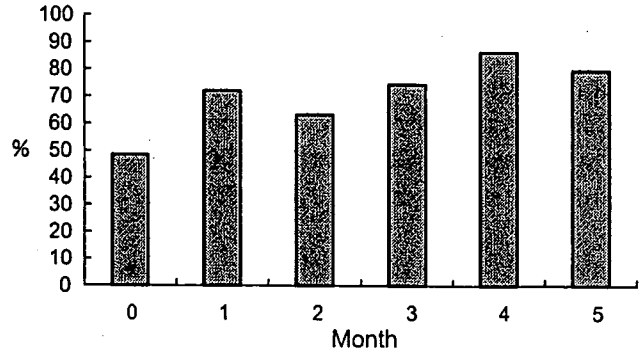


Fig. 2. Percentages of bilateral spontaneous smiles by month.

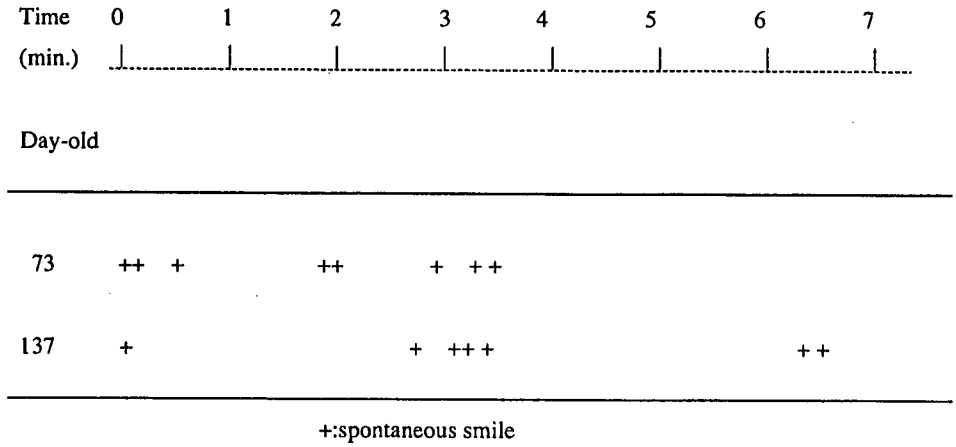


Fig. 3. Smiles bursts.

2.2. *Spontaneous laugh*

Fifteen spontaneous laughs, from 11- to 181-day-old, were observed. The mean duration of spontaneous laughs was 4.37 s (S.D. = 1.89). The mean duration of spontaneous laughs was longer than that of spontaneous smiles [$F(1, 578) = 28.34$, $p < .001$]. There was no developmental change in the duration of spontaneous laugh.

The laterality of one spontaneous laugh could not be determined because he was sleeping on his stomach. Thirteen out of 14 spontaneous laughs were bilateral. One unilateral spontaneous laugh (left side of the face) was observed at 133-day-old.

2.3. *Smile bursts*

Takai (2005) defined the bursts of spontaneous smiles as a "period of more than 7 spontaneous smiles in 7 min". In the longitudinal study on one male infant's first 6-months, Takai (2005) found seven smile bursts.

Fig. 3 shows the smile bursts of this study. Two smile bursts, at 73 and 137-day-old, were found.

3. Discussion

First, we should recognize that we observe spontaneous smiles even in the 6th month (mothers reported to us that they observed them after the 12th month). Kagan and Fox (2006) noted: "... the 1st year consists of two important transitions. One occurs at 2–3 months, and the second at 7–12 months of age. The first transition is accompanied by disappearance of newborn reflexes, endogenous smiling, ... (p. 169)". The results of this study prove that the description on spontaneous smiles in the influential handbook should be changed. At 2 months, infants show socially elicited smiles (Rochat, 2001). Spontaneous smiles and social smiles coexist during infant periods. Spontaneous smiles

do not transform into social smiles. These might be the most important results of this longitudinal study. Our positive emotions may have several roots.

From Fig. 2, the rise of bilateral smiling began at the 2nd month. Kawakami et al. (2006) discussed that developmental changes in the brain might cause this phenomenon. By the development of cerebral control, unilateral spontaneous smiles may be changed to bilateral spontaneous smiles. For this child, dramatic changes appeared at the 2nd month. By analyses of the brain at the time of spontaneous smiles, especially at the time of "smile bursts", we will learn some phases of developmental changes.

The asymmetrical tonic neck reflex (ATNR) is observed during the first 2 or 3 months of life, and it is usually integrated by 6 or 7 months (Snow, 1989). Can we relate the results of Fig. 1 to ATNR? Both Hauser (1993)'s rhesus monkeys and Holowka and Petitto (2002)s' human infants showed right hemisphere dominance for the production of facial expression. There was no dominance of lateralities in this study. This is a case study, so we need to study more cases to generalize the results.

Waller and Dunber (2005) observed silent bared teeth display (smiling-like) and relaxed open mouth display (laughing-like) in chimpanzees, and they discussed the differences of the two displays. Their morphological definitions of "smiling-like" and "laughing-like" displays are a little different from ours. The results of this study show that the durations of spontaneous laughs were longer than those of spontaneous smiles, and almost all of spontaneous laughs were bilateral as shown by Kawakami et al. (2006). Only one spontaneous laugh was unilateral in this case. This unilateral spontaneous laugh was observed at 133-day-old. Kawakami et al. (2006) claimed that "Spontaneous smile" and "Spontaneous laugh" might be different behaviors from the beginning. We confirmed this claim by the results of this study. To study the origins of spontaneous smiles and spontaneous laughs, it might be necessary to observe premature babies and to watch fetuses using a three-dimensional ultrasound scope.

To compare the frequencies of spontaneous smiles by weeks/months, fixed schedules of observation may be better using many participants.

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Development of the Laryngeal Air Sac in Chimpanzees

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Abstract Though many nonhuman primates possess a laryngeal sac, the great apes are unique in their great size. Though an enlarged sac probably arose in their common ancestor, its functional adaptations remain a matter of debate. Its development in extant great apes is likely to provide valuable information to clarify the issue. We used magnetic resonance imaging to examine the development of the laryngeal sac in 3 living chimpanzees, age 4 mo–5 yr, and identified 2 distinct growth phases of the sac. A gradual growth of the sac in early infancy results in a configuration so that it occupies the ventral region of the neck; many adult non-hominoid primates having a sac show the configuration. The subsequent rapid expansion of the sac in late infancy causes the final configuration in chimpanzees, wherein the sac expands into the pectoral, clavicular, and axillary regions. The latter phase possibly arose at latest in the last common ancestor of extant great apes and contributed to the evolution of the enlarged sac, despite the later evolutionary diversification in adult sac anatomy and growth. As many studies have advocated, the enlarged sac probably plays a role in vocalization in adults. However, physiological modifications in the laryngeal region during infancy are likely to provide valuable information to evaluate the functional adaptations of the enlarged sac in the great apes.

Keywords magnetic resonance imaging · *Pan troglodytes* · ventricular sac · vocalization

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Introduction

Many species of nonhuman primates have a laryngeal air sac, an accessory mucosal membrane pouch growing out from the laryngeal region (Hayama 1970; Hewitt *et al.* 2002; Negus 1949; Starck and Schneider 1960). There are 5 forms among nonhuman primates, based on the anatomy of the opening to the laryngeal region (Hayama 1970). Though there are controversies regarding the distributions of forms of air sacs among primates (Hewitt *et al.* 2002), all great apes and siamang definitely share 1 type: a ventricular sac that extends ventrally from bilateral laryngeal ventricles to fuse in front (Hayama 1970; Hewitt *et al.* 2002; Negus 1949; Starck and Schneider 1960). By contrast, other gibbons and humans have bilateral laryngeal ventricles, but no true laryngeal sac (Fitch 2000; Hayama 1970, 1996; Hewitt *et al.* 2002; Némai and Kelemen 1933; Negus 1949; Starck and Schneider 1960). The great apes are unique in having an enlarged sac extending into the pectoral and axillary regions (Avril 1963; Brandes 1932; Hayama 1970; Hewitt *et al.* 2002; Kleinschmidt 1938; Negus 1949; Raven 1950; Starck and Schneider 1960), though many other primates have a smaller sac, at the largest extending to the ventral region of the neck (Hayama 1970; Hewitt *et al.* 2002; Negus 1949; Starck and Schneider 1960).

In chimpanzees, the bilateral sacs fuse with each other in front of the region between the hyoid bone and the thyroid cartilage (Avril 1963). The fused sac expands superiorly to form an unpaired recess at the dorsal aspect of the hyoid body (hereafter, the hyoidal recess). Inferiorly, it forms a long unpaired recess along the ventral aspect of the laryngeal cartilages and trachea to reach the sternum (hereafter, suprasternal recess). From here, the sac expands further to form an unpaired recess at the ventral aspect of the pectoral region (hereafter, presternal recess) and bifurcates to form bilateral recesses extending into the infraaxillary regions (hereafter, axillary recesses).

The exact functions and evolutionary adaptations of the enlarged sac in the great apes remain matters of debate (Fitch and Hauser 2003; Hewitt *et al.* 2002;). The enlarged sac likely arose at the latest in the last common ancestor of the extant great apes, an evolutionary step that possibly involved changes in the rate or timing of existing developmental processes or novel growth processes (Gould 1977; McKinney and McNamara 1991; Rice 2000). Therefore, the changes in physiology that accompany distinct developmental events contributing to the formation of the enlarged sac in extant subjects are likely to shed light on its original functions. Unfortunately, there is little information on the growth of the laryngeal air sacs in great apes (Table I; Avril 1963; Brandes 1932; Huber 1931; Kleinschmidt 1938). We used magnetic resonance imaging (MRI) to examine the growth of the laryngeal air sac in 3 living chimpanzees age 4 mo–5 yr.

Methods

We studied 3 chimpanzees: Ayumu (male), Cleo (female), and Pal (female). They were born in 2000, and the biological mothers reared them in the Primate Research Institute, Kyoto University (PRI; Matsuzawa 2003). We took sagittal tomographic

images of their necks at PRI via a General Electrics Signa Profile MRI scanner (.2 Tesla), at scheduled intervals from 4 mo to 5 yr of age (Table II). The MRI protocol and experimental procedure in this study are per Nishimura *et al.* (2003, 2006). We anesthetized the subjects intramuscularly with a mixed solution containing 3.5 mg of ketamine hydrochloride (Sankyo, Tokyo) and .035 mg of medetomidine hydrochloride (Meiji Seika Kaisha, Tokyo) per kg of body mass, but we sedated subjects>4 yr orally with 3.75 mg of droperidol (in 1.5 ml) before anesthetization. We scanned them, placing them supine with their heads fixed to the coil with belts. All imaging sequences are sagittal spin echo series with fields of view of 18–28 cm, with 2.7 mm or 3 mm slice thicknesses and .8 mm or .5 mm gaps between slices (Table II). The matrix of all MR images is 256×256 pixels, and image resolutions ranged from .7×.7 to 1.09×1.09 mm/pixel. Care and use of the subjects adhered to the guidelines of the PRI (1986, 2002), and the Ethics Panel of the PRI approved the MRI examination protocol.

We measured the linear dimensions of the laryngeal air sac on MR images transferred to a personal computer via ImageJ software (W. Rasband, National Institutes of Mental Health, Bethesda, MD; http://rsb.info.nih.gov/ij/). Standard planes on the midsagittal plane were as follows: VLT, ventral line of the trachea; ACG, the level of the anterior commissure of the glottis; SSt, superiormost level of the sternum. Definitions and illustrations are in Table III and Fig. 1, respectively. The measurements included L_H, the length of the hyoidal recess, parallel to VLT from the superiormost to the inferiormost points of a growing sac before it reached the ACG, or its length to the ACG after the sac had already grown below it; L_S, the

Table I Morphological studies on the laryngeal sir sac in great apes

Species	Studies	Sex	n[a]	Developmental stages (sample size)[b]
Pongo pygnaeus	Brandes (1932)	Male	14	Adult (10), adolescence (1), juvenile (1), neonate (1), 5 yr (1)
		Female	6	Adult (4), adolescence (1), juvenile (1)
		?	1	2 mo (1)
	Avril (1960)	Female	1	10 yr (1)
	Hayama (1970)	Male	2	Adolescence (2)
		Female	3	Adult (1), adolescence (2)
Gorilla gorilla	Kleinschmidt (1938)	Male	1	10 yr (1)
	Raven (1950)	Male	1	Adult (1)
	Hayama (1970)	Male	1	Adult (1), adolescence (1)
		Female	1	Adult (1), adolescence (1)
Pan troglodytes	Avril (1963)	Male	3	Infant (1), juvenile (1), 15 yr (1)
		Female	4	Fetus (1), infant (1), 6 yr (1), 9 yr (1)
		?	3	Juvenile (1), probably infant (2)
	Hayama (1970)	Male	1	Adolescence (1)
		Female	3	Adult (1), adolescence (2)
	present study	Male	1	4 mo–5 yr[c] (1)
		Female	2	4 mo–5 yr[c] (2)

2?=unknown

[a] Total sample size for each study.

[b] Developmental stages of the subjects and sample size at each stage. If known, chronological age of each subject at the time of study.

[c] We examined the subjects longitudinally, as in Table II.

Table II Ages of the subjects at the times of scans, parameters of MRI scanning, and measurements of dimensions

Subjects	Age (mo)	Pixel sizes[a] (mm/pixel)	FOV (mm)	Thickness (inter-slice gap)[b] (mm)	L_H (mm)	L_S (mm)
Ayumu	4	.74	190	2.7 (.8)	8.29	absent
	6	.70	180	3.0 (.5)	9.90	.49
	9	.74	190	2.7 (.8)	12.34	1.48
	12	.70	180	3.0 (.5)	15.34	2.33
	18	.70	180	3.0 (.5)	15.85	3.12
	22	.90	230	2.7 (.8)	15.74	4.36
	25	.86	220	3.0 (.5)	17.58	3.04
	30	.98	250	3.0 (.5)	18.48	8.15
	36	1.09	280	3.0 (.5)	21.42	14.32
	42	.98	250	3.0 (.5)	2.89	54.22[d]
	48	.98	250	3.0 (.5)	21.50	53.55[d]
	52	.98	250	3.0 (.5)	19.30	53.82[d]
	54	.98	250	2.7 (.8)	26.77	—
	60	.98	250	3.0 (.5)	28.05	—
Cleo	4	.70	180	3.0 (.5)	7.04	1.12
	6	.70	180	3.0 (.5)	1.25	.43
	9	.70	180	3.0 (.5)	8.58	1.37
	12	.74	190	2.7 (.8)	1.36	2.18
	18	.70	180	3.0 (.5)	1.86	1.96
	25	.86	220	3.0 (.5)	14.37	9.86
	31	.98	250	3.0 (.5)	18.50	38.84[d]
	36	.98	250	3.0 (.5)	18.71	39.90[d]
	43	.98	250	3.0 (.5)	21.33	—
	48	.98	250	3.0 (.5)	25.87	54.71[d]
	54	.98	250	3.0 (.5)	27.86	—
	60	.98	250	3.0 (.5)	29.69	—
Pal	4	.70	180	3.0 (.5)	9.21	absent
	6	.74	190	2.7 (.8)	1.44	.23
	9	.70	180	3.0 (.5)	8.44	2.88
	12	.70	180	3.0 (.5)	11.45	6.99
	18	.70	180	3.0 (.5)	13.78	9.67
	24	.86	220	3.0 (.5)	16.16	42.03[c]
	30	.98	250	3.0 (.5)	15.32	—
	36	.98	250	3.0 (.5)	18.97	48.82[d]
	42	.98	250	3.0 (.5)	17.84	5.82[d]
	48	.98	250	3.0 (.5)	22.23	—
	54	.98	250	3.0 (.5)	22.00	61.63[d]
	60	.98	250	3.0 (.5)	25.48	—

L_H=length of the hyoidal recess of the laryngeal sac; L_S=length of suprasternal recess of the laryngeal sac; absent=the suprasternal recess had not developed; —=no measurements because the landmarks were outside the image field.

[a] The values varied irregularly during infancy, but had little influence on the accuracy of measurements.

[b] This means that the slice interval of all scans was 3.5 mm, regardless of differences in slice thickness and interslice gap.

[c] The sac almost reached the superior edge.

[d] The sac had already expanded beyond the superior edge of the sternum.

length of the suprasternal recess, parallel to VLT, from the ACG to the inferiormost point of the growing sac before it reached the SSt, or the length to the SSt after the sac grew beyond that level (Fig. 1).

Table III Definitions for the standard planes used

Landmarks and planes	Abbr.	Definition
Level of the anterior commissure of the glottis	ACG	The line perpendicular to the VLT from the anterior commissure of the glottis at the base of the epiglottis
Superiormost level of the sternum	SSt	The line perpendicular to the VLT and tangential to superior surface of the sternum
Ventral line of the trachea	VLT	The most ventral straight line of the trachea

Results

We obtained good MR images showing the longitudinal growth in the laryngeal air sac for each subject (Fig. 2), though for Ayumu at 4 and 6 mo, the images are slightly obscure because of motion artifacts. Nevertheless, all the images were adequate for the evaluation of anatomical development (Table II; Fig. 3).

We identified a small pouch at the dorsal aspect of the body of the hyoid at 4 mo for all 3 subjects (Figs. 2a, 3). The sac expanded superiorly in the dorsal area of the hyoidal body and inferiorly to the level of the anterior commissure of the glottis by 6 mo at the latest, for all subjects (Fig. 3). The air sac continued to expand superiorly to occupy the entire dorsal area of the hyoidal body in the first year of life (Figs. 2b, 3). It gradually expanded inferiorly to sit along the ventral aspect of the laryngeal cartilages in early infancy, despite variations in growth rates (Figs. 2b, 3).

In all subjects, in late infancy the sac grew rapidly below the ventral aspect of the trachea to reach and extend beyond the superior edge of the sternum (Figs. 2c, 3): after 1.5 yrs for female Pal, after 2.5 yr for female Cleo, and after 3.5 yr for male Ayumu (Figs. 2c, 3). The supra-and presternal recesses of the sac then widened greatly (Fig. 2d). We did not evaluate further expansions of the sac into the pectoral, clavicular, or axillary regions, which we did not image.

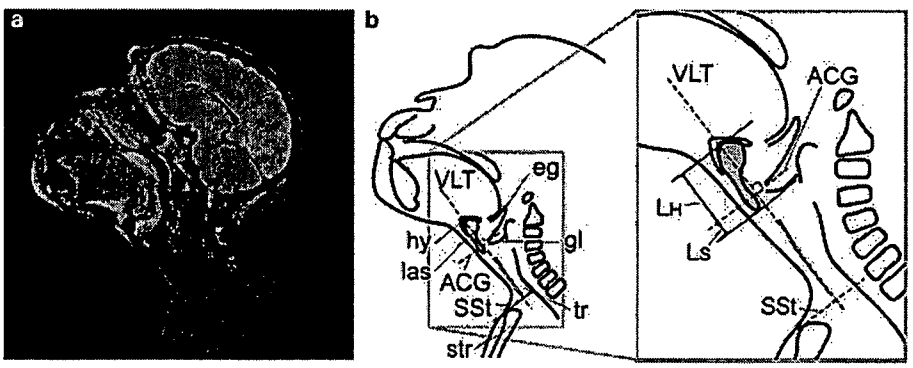

Fig. 1 Diagram of measurements of the laryngeal air sac. (a) Magnetic resonance (MR) image. (b) Lengths of the hyoidal recess (L_H) and the suprasternal recess (L_S) of the laryngeal sir sac (las). ACG= level of the anterior commissure of the glottis; SSt=superior-most level of the sternum; VLT=ventral line of the trachea (see also definitions in Table III); eg=epiglottis; gl=glottis; hy=hyoid bone; str=sternum; tr=trachea.

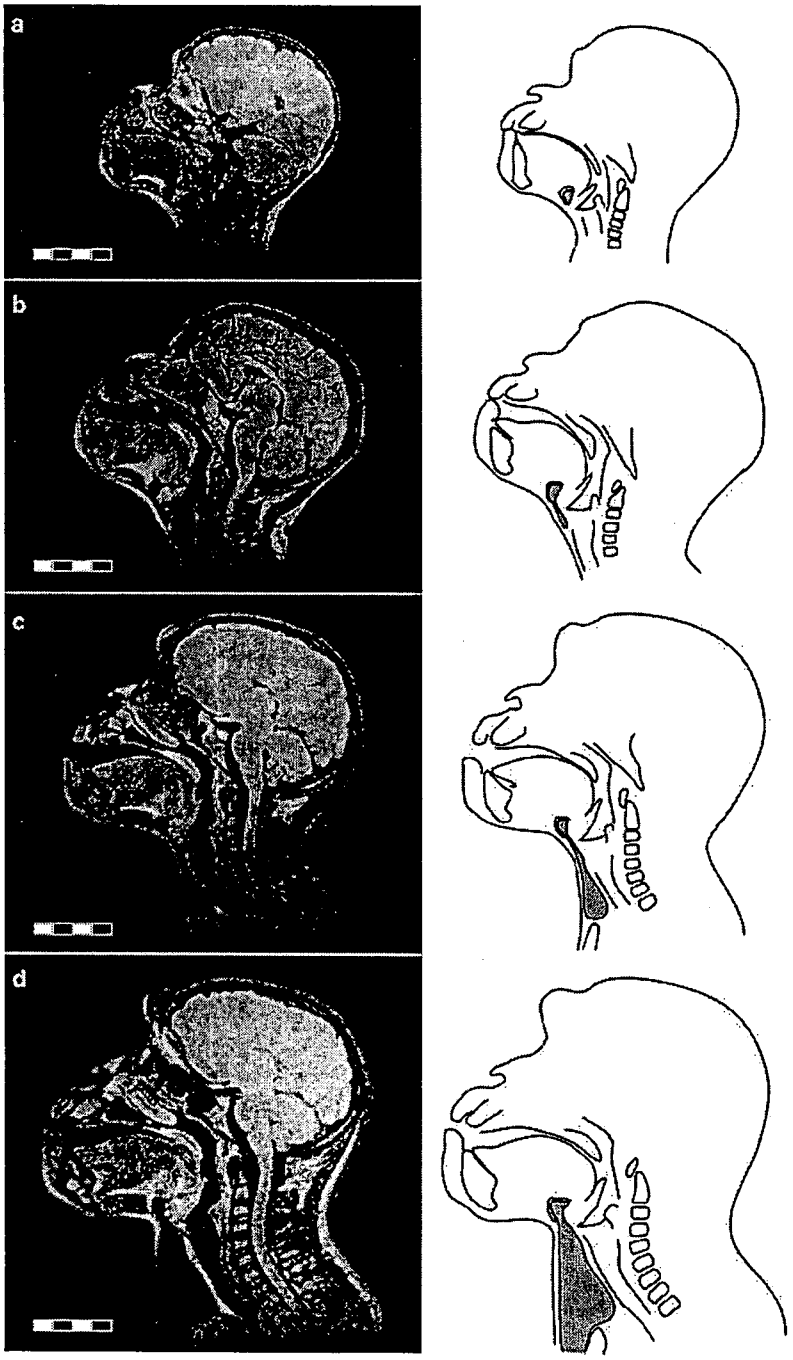

Fig. 2 MR images of the laryngeal air sac for the same female chimpanzee (Pal). (a) At 4 mo, a small pouch had formed in the dorsal area of the hyoid bone. (b) At 18 mo, the sac occupied the entire area dorsal to the hyoid bone and inferior to the ventral aspect of the laryngeal cartilages. (c) At 24 mo, the sac had expanded to reach the sternum. (d) At 48 mo, the sac had expanded inferiorly into the ventral aspect of the pectoral regions and had widened at the level of the trachea. Scale in cm.