れる看護援助について考察する.

研究方法

本研究は, 質的記述的研究であり, 診療録からデータを収集し, 内容分析を行った.

1 対象患者

2009年1月ー2010年12月の間に, 関東圏のがん専門病院において胸部食道がん根治的手術を受けた患者で, 開腹・開胸, 腹腔鏡・胸腔鏡による術式または補助下術式も含むものとした. 再建術式の種類, 手術前後の化学療法・放射線療法の有無は問わず, すべて含めることとした. ただし, 永久気管孔を造設した患者, 二期的手術を受けた患者は除外した.

2 データの収集方法

関東圏のがん専門病院の食道外科外来における診療録から, 以下のデータを収集した.

1) 対象の背景 : 対象属性, 術後の症状・徴候・処置

2) 知覚している困難 : 困難の内容は, 食道外科外来の看護師が記載した看護記録から収集した

2) の看護記録は, 診療の一部として記載されたものであるが, 以下のように意図的な試みにおける記録である. 研究施設において胸部食道がん患者に対する外来看護ケアを検討するために, 文献検討を行い, 想定される患者の多様な症状と訴え・相談内容の推移について, 質的な内容を詳細に記述できる看護記録を作成した. それを活用し, 食道外科外来における医師の診察前または診察後に, 看護師が患者全員に対し半構造的な問いかけを行い, 患者の回答・反応を看護記録に記述した. 本研究で抽出したデータは,「身体的・心理的・社会的に今つらいこと, 対応に困っていること, 心配なことは何か」の問いかけの部分である. 担当した看護師は, 患者が回答した内容について対応後に詳細に記載した.

この試みに対応した看護師は2名であり, いずれもがん専門病院における看護師経験が10年以上あり, 1名は摂食・嚥下障害看護認定看護師, もう1名はがん性疼痛看護認定看護師資格を有していた.

3 データの分析方法

データの分析は, 症状・徴候, 処置については, 単純集計を行った. 患者の生活における困難は, 内容分析の手法[14]を参考に, 以下の手順で分析した.

①看護記録に記載されている胸部食道がん術後患者の訴えた困難を抽出した.

②意味内容をもつ記録単位に分割した.

③記録単位の意味内容を損なわないように内容を要約しコードを作成した.

④類似性をもとにコードをまとめてカテゴリを作成した.

データの真実性を高めるために, 看護記録の記述からの分析過程について, 他者が妥当性を判断できるように記録を残した. また, コードがどのカテゴリに該当するか判定するために, がん看護の経験が10年以上の2名の看護師により分析を行った. さらに全体を通して, 看護学研究者による確認を行いながら進めた.

本研究は日常で行われている診療の内容についての診療録調査であり, 研究実施施設の研究倫理審査委員会の承認を得て, 実施された.

研究結果

1 対象患者の属性, 術後の症状・徴候・処置 (表1)

対象となった患者は根治的胸部食道がん手術を受けた66名であり, 男性58名 (87.9%), 年齢中央値69歳 (範囲49ー88歳) であった. 食道がん根治術のアプローチは, 開胸 (50.0%) による食道亜全摘 (40.9%), 三領域リンパ節郭清 (92.4%), 胃管 (90.9%) による後縦隔経路再建 (83.3%) が最も多かった. 術後の入院期間は, 中央値17.5日 (範囲10ー143日) であった. 21名 (31.8%) の患者が退院時に腸瘻を有していた.

対象患者の外来受診時期は, 退院後中央値2.3カ月 (範囲2週目ー12カ月目), 受診回数は中央値3回 (範囲1ー7回) であった.

反回神経麻痺を認めた患者は, 29名 (43.9%) であった. そのうち, 術後1病日目に診断された患者は27名, 食事開始時に診断された患者は2名であった. 処置や時間的経過で17名は改善した. しかし, 食事開始時の麻痺患者は12名 (18.2%) となっていた.

縫合不全患者は16名 (24.2%) であった. 退院時の食事摂取カロリーは, 56%が1,000kcal未満であった. 吻合部狭窄や通過障害に対し, 食道拡張術の処置を経験した患者は20名 (30.3%) であり, そのうち4回以上の処置が行われた者は9名 (45.0%) であった. 初回の食道拡張術は, 術後1カ月以上の患者が18名 (90%) であり, また退院後に初回の食道拡張術を実施した患者は14名 (70%) であった. 縫合不全を経験した患者のうち食道拡張術実施患者は12名であり, 縫合不全を経験しなかった患者よりも有意に高かった ($p<0.001$).

食事開始時に, 摂食・嚥下障害看護認定看護師に摂食・嚥下に関する介入依頼があった患者は12名 (18.2%) であった. このうち, 術後に反回神経麻痺のあった患者は11名, 反回神経麻痺を認めなかったが食事時に咳き込みの強い患者は1名であった.

2 胸部食道がん術後患者の退院後の生活の困難

胸部食道がんの手術を受けた66名の患者が外来において看護師に相談した内容の記録単位は221抽出され, 患者が訴えた困難のカテゴリは25, コードは65に分類された (表2). 以下, カテゴリを「 」に, コードを『 』に提示し, 結果の概要を解説する.

胸部食道がんの手術を受けた患者は,「反回神経麻痺に伴い会話が難しい」状態や「反回神経麻痺に伴い嚥下時の不快がある」状態など, 会話時や嚥下時の不快を訴えていた.

食事に関しては, 患者から「摂食時のつかえにより不快がある」「食後に不快な症状がある」「食事摂取量の増加が難しい」「摂食・嚥下習慣の変更が難しい」などの訴えがあった. 具体的には『つかえ感がある』ことを自覚し, 特に『固形物でつかえる』と看護師に相談していたり, 食後に『のどの停滞感がある』ことや,『げっぷが出にくい』苦痛を訴えたりしていた. また,『食欲低下がある』『空腹感がない』ことで, 食事量が増加できない状況があった. 手術前までの嚥下方法の習慣を変更す

表 1　胸部食道がん根治術を受けた対象患者の背景 (n=66)

			n (%)	中央値 (範囲)
男性			58 (87.9)	
女性			8 (12.1)	
年齢 (歳)				69 (49～88)
補助療法	術前治療	Chemo-radio therapy (CRT)	4 (6.1)	
		Docetaxel, cisplatin, 5-fluorouracil (DCF)	4 (6.1)	
		Cisplatin, 5-fluorouracil (FP)	18 (27.3)	
		その他	1 (1.5)	
	術後治療	FP	3 (4.5)	
		その他	4 (6.0)	
術式	アプローチ	開胸術	33 (50.0)	
		開胸開腹術	12 (18.2)	
		非開胸	6 (9.1)	
	(再掲)	胸腔鏡補助下 (VATS)	25 (37.9)	
	切除部位	食道亜全摘	27 (40.9)	
		食道切除	22 (33.3)	
		食道抜去	7 (10.6)	
	リンパ節郭清	三領域	61 (92.4)	
		二領域またはそれ以下	4 (6.1)	
	再建法	後縦隔経路	55 (83.3)	
		その他 (後胸骨経路 等)	11 (16.7)	
	再建臓器	胃管	60 (90.9)	
		その他 (十二指腸, 結腸)	6 (9.1)	
術後入院期間		10～14 日	25 (37.9)	17.5 (10～143)
		15～30 日	23 (34.8)	
		31 日以上	18 (27.3)	
食事開始の術後日数		5～10 日	41 (62.1)	8 (5～88)
		11～29 日	13 (19.7)	
		30 日以上	10 (15.2)	
反回神経麻痺		術後 1 日目の内視鏡による麻痺所見あり	27 (40.9)	
		食事開始時の透視造影による誤嚥所見あり	12 (18.2)	
		退院後の不顕性誤嚥あり	1 (1.5)	
縫合不全の時期 (頸部吻合部)		術後 1 週間未満	5 (7.6)	
		術後 1 週間～2 週間未満	7 (10.6)	
		術後 2 週間以降	5 (7.6)	
退院時の経口摂取カロリー		0～500kcal 未満	9 (13.6)	
		500～1,000kcal 未満	28 (42.4)	
		1,000～1,500kcal 未満	10 (15.2)	
		1,500kcal 以上	19 (28.8)	
腸瘻造設の状況		退院時における腸瘻造設あり	21 (31.8)	
食道拡張術		あり	20 (30.3)	
初回実施の術後日数		1 カ月未満	2 (10.0)	
		1～2 カ月未満	8 (40.0)	
		2 カ月以降	10 (50.0)	
初回実施の退院後日数		退院前	6 (30.0)	
		1 カ月未満	4 (20.0)	
		1～2 カ月未満	5 (25.0)	
		2 カ月以降	5 (25.0)	
実施の頻度		1～3 回	11 (55.0)	
		4～6 回	4 (20.0)	
		7～10 回	3 (15.0)	
		11 回以上	2 (10.0)	
外来受診の時期 (退院後週・月数)				2.3 カ月 (2 週～12 カ月)
外来受診の回数				3 (1～7)

*一部のデータに , 不明や欠損値が含まれる .

表２　胸部食道がん術後患者の退院後の生活における困難

カテゴリ	コード
反回神経麻痺に伴い会話が難しい	嗄声がある
反回神経麻痺に伴い嚥下時の不快がある	食事に伴うむせがある 流動物によるむせがある 食後に咳・痰が増加する
摂食時のつかえにより不快がある	つかえ感がある 固形物でつかえる つかえがあるためカプセル薬が内服できない
食後に不快な症状がある	のどの停滞感がある げっぷが出にくい 食後に調子が悪い
食事摂取量の増加が難しい	食欲低下がある 空腹感がなく食事の時間に迷う 経腸栄養や食前薬で満腹になる 食べられる量が増えない 食事摂取量の適量が分からない
摂食・嚥下習慣の変更が難しい	分割食が難しい 早食いが持続している 特殊な嚥下法が負担になる
消化液逆流に伴い不快がある	消化液の逆流に伴う不快がある 消化液の夜間逆流に伴う不快がある 消化液の逆流に伴う夜間の不眠がある 摂食量の増加で消化液の逆流量が増える 食後に逆流予防のために横になれないので辛い
経腸栄養注入に関する不快がある	経腸栄養注入時に気分不快がある 経腸栄養カテーテル挿入部・抜去部の皮膚障害がある 経腸栄養カテーテルの違和感・不快がある
経腸栄養管理に関する負担がある	経腸栄養カテーテル管理が負担である
呼吸器症状に関する不快がある	息苦しさがある 咳や痰の喀出が難しい 身体活動で息切れがある
排泄に関する不快がある	食事の種類・量で下痢となる 便秘がある 便を出す力が出ない 放屁が頻回にある
疼痛による不快がある	胸部痛がある 腹痛がある 創痛がある
体重減少がある	体重が増えない 食べても体重が増えない
疲労感がある	疲労感がある 食べ過ぎると疲れる 活動量を増やすことで疲れる
飲酒・喫煙ができない不快がある	禁酒のため楽しみが減った 飲酒しないので不眠となる
身体活動の拡大が難しい	身体活動にて苦痛が増す (息苦しさ, 痛み) 運動のペースがつかめない 食事時間が長く外出できない １人では運動できない
職場復帰に伴う悩みがある	休職期間について悩む 体力がないので復職を躊躇したり復職時期に悩む 食事摂取量が増えない中での仕事復帰に不安がある
体調が改善しない不安がある	体重が増えない不安がある 症状が改善しない不安がある 自分だけ体調が悪いのかと不安がある
体調が改善しないのをあきらめる	改善しない症状に慣れるしかないと思う 改善しない症状は我慢するしかないと思う
対処方法が現状でよいか自信がない	自分の対処でいいのか不安がある 医師の方針のように動けない不安がある 経腸栄養中止にて栄養面で不安がある
セルフモニタリングの実施が辛い	体重減少が分かるので測定するのが苦痛である
再発への不安がある	再発の不安がある
意思決定への迷いがある	追加治療の決定に迷う
家族の負担を心配する	家族の介護負担が気になる 家族の心労が気になる
療養のための費用負担が多い	健康補助食品のコストがかかる

ることについては,『分割食が難しい』『早食いが持続している』『特殊な嚥下法が負担になる』などの困難な状況が示された.

また患者は,「消化液逆流に伴い不快がある」と感じており,その影響から,『消化液逆流に伴う夜間の不眠がある』と看護師に訴えていた.

退院時に経腸栄養を持続したまま生活している患者は「経腸栄養注入に関する不快」や「経腸栄養管理に関する負担がある」と訴えていた.具体的には,経腸栄養注入による気分不快を訴えたり,カテーテル挿入部・抜去部の皮膚障害に困難を感じたりしていた.また,カテーテルの取り扱いに関する困難もあった.

患者は,「呼吸器症状に関する不快がある」「排泄に関する不快がある」「疼痛による不快がある」「体重減少がある」「疲労感がある」などの多様な症状を有していた.呼吸器症状としては,『息苦しさがある』『咳や痰の喀出が難しい』,排泄に関することとしては,下痢や便秘,疼痛として,胸部痛,腹痛,創痛の訴えがあった.また,体重減少や多様な状況による疲労感の訴えがあった.

手術を受けるために禁酒・禁煙をしていた患者では「飲酒・喫煙ができない不快がある」状況が示され,そのことで生活の楽しみが減ったり不眠に悩まされたりするなどの訴えがあった.

患者は,退院後に身体活動量の増加の必要性を指導されているものの「身体活動の拡大が難しい」状況があった.それは,『身体活動にて苦痛が増す』ことや『運動のペースがつかめない』状況などであった.

また,体調の回復に伴い「職場復帰に伴う悩みがある」状況があり,どの程度で復帰できるのかと『休職期間について悩む』状況があった.特に『体力がないので復職を躊躇したり復職時期に悩む』と,回復状況と仕事の作業量をふまえた不安の訴えがあった.

さらに「体調が改善しない不安がある」「体調が改善しないのをあきらめる」「対処方法が現状でよいか自信がない」「セルフモニタリングの実施が辛い」「再発への不安がある」などの不安の訴えがあった.具体的には,体重減少や症状が改善されない不安,つかえは慣れるしかない,自己判断や指示を受けて行っている行動が妥当であるか判断しかねる状況,体重のセルフモニタリングにより日々体重減少を認識する辛さ,再発への不安等,多様な状況が示された.

術後の補助療法実施の「意思決定への迷いがある」患者もいた.また,患者は家族の介護負担や心労を気にして「家族の負担を心配する」状況が示された.健康補助食品の費用に関する訴えなど「療養のための費用負担が多い」困難が示された.

考　察

本研究では,日本における胸部食道がん患者の典型的な術式を受けた患者66名を対象とし,胸部食道がん術後1年以内の退院後の生活における困難について,診療録より抽出・分析した結果,25カテゴリの困難に分類され,その実態を明らかにすることができた.

1 反回神経麻痺に伴う困難とケア

対象患者は,食事開始時にも12名(18.2%)が反回神経麻痺を有しており,これらの患者への誤嚥予防のケアの必要性が示唆された.長期的には,日本における胸部食道がん術後の反回神経麻痺の発生率は,約2割から8割強と幅があり[9,10],回復には術後半年程度かかると報告されている.今回の結果から,麻痺が発生している患者は嗄声やむせ,飲み込みにくさなどの困難を経験していた.さらに,明らかなむせは見られなくても,不顕性誤嚥のリスクも考慮する必要がある.患者は,長年の食行動における「摂食・嚥下習慣の変更が難しい」状況があり,その中には,『特殊な嚥下法が負担になる』という困難もあった.これらの状況をふまえ,誤嚥予防のための特殊な嚥下法等については,患者の負担感を考慮しながら継続して関わっていくことが重要であると示唆された.また,長期間誤嚥の可能性があることをふまえ,外来で患者に接する看護師は,医師と連携して,退院後も継続的かつ系統的にアセスメントを行うことが重要である.

2 狭窄に伴う困難とケア

結果で示されたように,患者はつかえをあきらめるしかないと我慢していた状況が示された.つかえの発症時期について,今回の調査から,吻合部狭窄のために行われた消化管拡張術は70%が退院後であったことからも,消化管狭窄症状の多くが,退院後に徐々に悪化する症状であることが示された.このことからも,つかえの症状は,外来における看護アセスメントの視点として重要であるといえる.また,「摂食時のつかえにより不快がある」患者は,固形物の摂取や内服に困難を感じていた.食道がん術後患者のつかえの症状が回復するには,欧米の調査によると術後1年以上必要であったと報告されているものもある[2,15].このように,つかえは長期にわたる症状であり,その間は栄養価の高い食事を効率的に摂ることが難しく,栄養不良となるリスクが問題となりうる.つかえの症状は頸部吻合部の狭窄などによってもたらされることが多いが,本研究の対象患者では,手術後の縫合不全のあった患者について有意に狭窄が生じ,食道拡張術の適応となっていた.術後に,頸部縫合不全を有した患者には,外来のフォローにおいて,狭窄のハイリスクになる可能性をふまえてアセスメントを行う必要がある.

3 消化液逆流に伴う困難とケア

今回の結果から,対象患者は逆流が継続している不快を訴えており,また消化液の逆流に伴い夜間の不眠がもたらされ,患者の苦痛が増強されていた.対象患者は,回復に伴い『摂食量の増加で消化液の逆流量が増える』ことで,逆流の症状が強くなっていた.先行研究では,食道がんの手術後期間の経過とともに悪化し,術後3年を経過しても75%の患者に逆流の問題があったとする報告[1]もある一方で,術後半年は25%の患者に発症が見られたが,術後1年で症状がほぼ回復したとする報告[2]もあった.いずれにしても,逆流の状態を長期的に観察し,回復により食事摂取量が増加するとともに消化液が増加し症状の悪化する可能性があることや,逆流は不眠ともなることをふまえ,患者に及ぼす影響をアセスメントして支援していく必要がある.

4 腸瘻造設に伴う困難とケア

今回の対象患者のうち,約32%の患者が腸瘻を有していたが,本研究結果からは,腸瘻を有して退院する場合には,その管

理に困難を有していることが示された. 退院時における患者の腸瘻の有無をアセスメントして, 家庭における管理状況を確認するとともに, 負担になっていることを受け止め関わることが重要である.

5 摂取カロリー増加に向けた困難とケア

本研究対象患者は, 手術後1カ月以内で70%以上が退院していた. 患者の退院時の経口摂取カロリーは, 過半数の患者が1,000kcal以下であり, 摂食・嚥下・消化・吸収機能が十分に回復していない時期の退院となっている実態が示された. 患者は, 退院後に摂取量を増加していく必要があるが, 食後の不快な症状として, のどの違和感, 満腹感, げっぷが出にくいなど, 食欲を低下させる要因に加え, 空腹感を感じないので時間を見ながら食べているなど, 経口摂取量の増加を阻害する要因が多様に見られた.

食事量を増加していくには, 退院後も, 患者の不快を緩和しながら, 経口摂取を増加するためのケアが重要であることが示された. 消化器症状は身体内部の障害によってもたらされるものであり, 患者が自覚症状を正確に把握して報告する必要がある. 外来の看護師は, 医師・栄養士などと協働しながら, また患者とその家族と継続的に関わりながら, より効果的な観察と患者に合った食生活上の対処法を探る必要がある.

6 身体活動と復職に対する困難とケア

今回の結果から, 対象患者は, 身体活動により苦痛が増し「身体活動の拡大が難しい」状況が示された. 先行研究によると, 食道がん術後患者は適応障害や抑うつ[16], 倦怠感[17]などを多く呈することが報告されている. このような患者に対し, 身体活動は, 精神面に及ぼす効果として不安や緊張の緩和, 抑うつのリスク低減等も認められている[18]. そのため, 多様な不安の中で過ごしている患者に, まずは身体活動が心身両面にとって重要であることを伝えることが大切である. そして, 身体活動は運動だけでなく, 家事や動物の世話など日常の生活活動も含まれる[19]ことを患者に説明し, 無理のない範囲で患者に合った身体活動の拡大を促すことが重要である. そのことにより, 長期的に継続できるような患者自身の取り組みを個別的に支援することが可能となる.

また「職場復帰に伴う悩み」として,『体力がないので復職を躊躇したり復職時期に悩む』実態が明らかにされた. 患者の身体活動の拡大とともに, 仕事の内容や患者を取り巻く支援体制の有無など, 患者の個別性をふまえた援助が必要であると考えられる.

7 心理的な特徴とケア

今回の結果から, 胸部食道がん術後患者の心理的な特徴も示された. たとえば,「体調が改善しない不安がある」「対処方法が現状でよいか自信がない」「再発への不安がある」など, 症状や体重が改善しない不安, 自分の対処でいいのか不安に感じる, などである. 患者は, このままでよいのかと, 現状について明確な見通しが欠如した状態の中で不安を感じていた. このように, 見通しの立たない“不確かさ”が続くと, 患者のストレスが高まるといわれており[20], 患者の訴えを医師・看護師をはじめ医療者がよく傾聴するとともに, 今後の見通しを説明したり, 患者が取っている行動の妥当性を承認したりするなどの関わりが求められる. また患者は「家族の負担を心配する」など, 家族の心身への負担を気にかけており, 家族を含めたケアが重要であることも示された.

結　論

今回の研究で, がんに関する専門性の高い看護師に対して患者が訴えた内容から, 胸部食道がん患者が術後1年以内に知覚する困難を明らかにすることができた. 術後長期間にわたる多様な困難は, その頻度や時期についても違いがあることが想定されるため, これらについて今後さらに研究を継続し, 術後の時期に応じた優先度の高いケアニーズを明らかにしていく必要がある.

今回示された患者の困難の中で, フィジカルアセスメントによる異常の早期発見, 生活習慣の変容へのアプローチ, 精神的なケアなど, 看護の介入で改善しうる内容も多いことが示された. これらの結果は, 患者の退院後の生活における困難を解決していくため, 今後の外来診療において看護師と医師・栄養士等が協働し, 患者・家族に合った医療を提供していくことの意義を裏づけるための, 貴重な臨床的基礎資料となりうる.

筆者らは, この結果をふまえ, 胸部食道がん術後患者の効果的な回復を支援するプログラムをさらに検討していく予定である.

本研究は, 厚生労働科学研究費補助金 (第3次対がん総合戦略研究事業)「上部消化器術後障害をもつがん患者の活力とQOL向上をめざすリハビリテーション開発」および公益財団法人高松宮妃癌研究基金「胸部食道がん術後の『退院後の生活』に安心と自信をもたらす患者指導法の開発」(研究課題番号: 12-24409) により実施したものである.

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著者の申告すべき利益相反なし

Original Research

Difficulties in daily life of post thoracic esophagectomy cancer patients after hospital discharge

Shigeaki Watanuki[1], Keiko Iino[2], Yurie Koyama[2], Miho Kurihara[3], Chisato Ichikawa[3], Kyoko Okada[3], Hideo Uesugi[3], Chie Asanuma[3], Hiroyuki Daiko[4], Takeo Fujita[4], Kyoko Suzuki[5], Chihoko Wada[5], Michiko Mori[6], Yoko Hisabe[7], Kaori Yagasaki[8] and Hiroko Komatsu[8]

1) Gerontological Nursing, National College of Nursing, Japan, 2) Adult Nursing, National College of Nursing, Japan,
3) Division of Nursing, National Cancer Center Hospital East, 4) Division of Esophageal Surgery, National Cancer Center Hospital East,
5) Division of Nursing, National Cancer Center Hospital, 6) Division of Nursing, Takasaki General Medical Center,
7) Division of Nursing, Tokyo Medical Center, 8) Faculty of Nursing and Medical Care, Keio University

Purpose: This study aimed at identifying difficulties among post thoracic esophagectomy cancer patients during outpatient follow-up. **Methods:** Patients who had radical esophagectomy at a cancer center hospital in Japan were prospectively observed and were interviewed by a certified nurse assigned at esophageal surgical outpatient division. Their responses were documented in medical records and were analyzed by content analysis method. This study was approved by the study hospital's research ethics committee. **Results:** The data from 66 patients were obtained. Content analysis yielded 221 extracts, 25 categories, and 65 codes of difficulties, including: concerns or signs/symptoms associated with dietary intake, physical activity, and anxiety. **Implications:** The majority of post-thoracoabdominal esophagectomy patients experienced multiple dysfunctions and symptoms after discharge. The results underscore the significance of nurses' role in assessing and instructing patients to address these issues.
Palliat Care Res 2014; 9(2): 128-35

Key words: thoracic esophageal cancer, difficulties in daily life, signs and symptoms, content analysis

Addiction
Research & Therapy

Nishizawa et al., J Addict Res Ther 2014, 5:2
http://dx.doi.org/10.4172/2155-6105.1000178

Research Article Open Access

Association between Genetic Polymorphism rs2952768, Close to the *METTL21A* and *CREB1* Genes, and Intellectual Ability in Healthy Subjects

Daisuke Nishizawa[1#], Kazutaka Ohi[2,3#], Ryota Hashimoto[2,4*], Hidenaga Yamamori[2,5], Yuka Yasuda[2], Michiko Fujimoto[2], Satomi Yano-Umeda[5], Masatoshi Takeda[2,4] and Kazutaka Ikeda[1*]

[1]*Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*
[2]*Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[3]*National Hospital Organization, Yamato Mental-Medical Center, Nara, Japan*
[4]*Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University, Hamamatsu University, Chiba University, and Fukui University School of Medicine, Osaka, Japan*
[5]*Department of Molecular Neuropsychiatry, Osaka University Graduate School of Medicine, Osaka, Japan*
[#]*These authors contributed equally*

Abstract

Objective: Human intelligence, which represents a set of cognitive abilities, is assumed to be a highly heterogenic trait. The Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies, and knowledge of the genes associated with IQ has continuously grown. Several previous reports indicated that IQ may be associated with addictive behaviors or the use of addictive substances, although the trend toward an association is not straightforward and depends on the substances abused. To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The rs2952768 single-nucleotide polymorphism (SNP) was recently reported to be associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, *CREB1*.

Methods: The present study used data from 298 biologically unrelated Japanese subjects. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. The rs2952768 SNP close to the *METTL21A* gene was extracted from this dataset. Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes.

Results: A significant effect of the SNP genotype was observed on current IQ (β = -2.27, p = 0.026). The number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores.

Conclusion: The present results suggest that the rs2952768 SNP, which was identified as a potent SNP associated with human opioid sensitivity, is also one of the genetic factors that contribute to human intellectual ability.

Keywords: Intelligence Quotient (IQ); Opioids; Addictive substances; Substance dependence; Single-nucleotide polymorphism (SNP); Cyclic adenosine monophosphate response element binding protein 1 (*CREB1*); Methyltransferase like 21A (*METTL21A*)

Introduction

Human intelligence, which represents a set of cognitive abilities, such as thinking, remembering, reading, learning, problem solving, and using language, is assumed to be a highly heterogenic trait. Intelligence Quotient (IQ) is the most widely used index for characterizing human intelligence in psychometric studies. It can be used to assess intellectual ability in not only healthy subjects but also in patients with disorders such as schizophrenia, autism, depression, and anxiety [1–3]. Among the well-examined genes are those involved in brain functions related to mechanisms of learning and memory, and genetic variations in such genes associated with IQ have been identified [4–6]. Knowledge of the genes associated with IQ has increased. A publicly available database explores IQ-associated human genes [7], revealing that IQ-associated genes are significantly enriched in multiple signaling events, especially those related to cognitive systems.

Several previous reports suggested that IQ can affect and also be affected by addictive behaviors or the use of addictive substances. For example, people with lower IQ scores are more likely to become cigarette smokers [8,9]. In a longitudinal study that assessed marijuana's impact on IQ, current marijuana use was found to be significantly and dose-dependently correlated ($p < 0.05$) with a decline in IQ over the ages studied [10]. High childhood IQ has generally been linked to alcohol dependence and more frequent alcohol consumption [11,12]. In a study that investigated demographic profiles related to estimations

***Corresponding authors:** Ryota Hashimoto, M.D., Ph.D., Associate Professor, Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University, Hamamatsu University, Chiba University, and Fukui University School of Medicine D3, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan, Tel: +81-6-6879-3074; Fax: +81-6-6879-3074; E-mail: hashimor@psy.med.osaka-u.ac.jp

Kazutaka Ikeda, Project Leader, Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan, Tel: +81-3-6834-2379; Fax: +81-3-6834-2390; E-mail: ikeda-kz@igakuken.or.jp

Received January 30, 2014; **Accepted** March 29, 2014; **Published** March 31, 2014

Citation: Nishizawa D, Ohi K, Hashimoto R, Yamamori H, Yasuda Y, et al. (2014) Association between Genetic Polymorphism rs2952768, Close to the *METTL21A* and *CREB1* Genes, and Intellectual Ability in Healthy Subjects. J Addict Res Ther 5: 178. doi: 10.4172/2155-6105.1000178

of Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale IQs (DP Estimated IQs), the DP Estimated IQ was found to be significantly related to the duration of opioid addiction, and a higher estimated IQ was associated with a shorter duration [13]. However, few studies have focused on genes or their functional involvement in the mechanism of addiction in the context of investigating genes related to human intelligence or IQ scores.

To explore the genetic factors that contribute to IQ, we conducted an association study of a genetic polymorphism, rs2952768. The potent rs2952768 single-nucleotide polymorphism (SNP) was recently associated with human opioid sensitivity and shown to be associated with the efficacy of opioid analgesics, severity of substance dependence, and mRNA expression levels of a neighboring gene, *CREB1* [14].

Materials and Methods

Subjects

The data from 298 healthy subjects (40.9% male [122/176]; mean age ± SD: 36.8 ± 12.4 years) were used in the present study. The subjects were all biologically unrelated and Japanese. The subjects were recruited through local advertisements at Osaka University. Psychiatrically, medically, and neurologically healthy subjects were evaluated using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), Non-Patient Edition (SCID-I/NP), to exclude individuals who had substance-related disorders, who had received psychiatric medications, or who had first- or second-degree relatives with psychiatric disorders. Additionally, subjects were excluded from the study if they had neurological or medical conditions that could potentially affect their central nervous system, such as atypical headaches, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures, or mental retardation. Written informed consent was obtained from all of the subjects after the procedures were explained. This study was performed in accordance with the World Medical Association's Declaration of Helsinki and approved by the Osaka University Research Ethics Committee.

Measurement of intellectual ability

Current low IQ may or may not be a determinant of drug and alcohol dependence or the use of addictive substances, and the tendency toward an association may be different between abused substances [8-13]. Based on our evidence that a genetic variant close to the methyltransferase like 21A (*METTL21A*) gene, rs2952768, is related to the severity of drug and alcohol dependence, we investigated the association between the rs2952768 genotype for drug and alcohol dependence and current IQ in healthy Japanese subjects. To assess current intellectual ability, we used verbal IQ from the Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) [15]. The subjects were assessed by trained clinical psychologists to obtain verbal IQ scores on the WAIS-III.

Single-nucleotide polymorphism genotyping

Venous blood was collected from the subjects, and genomic DNA was extracted from whole blood according to standard procedures. Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) as previously described [16]. The rs2952768 SNP close to the *METTL21A* gene was extracted from this dataset. No deviation from Hardy-Weinberg equilibrium (HWE) in the examined SNP was detected ($p = 0.10$).

Statistical analysis

Differences in clinical characteristics between the genotype groups were analyzed using the χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables using PASW Statistics 18.0 software (SPSS Japan, Tokyo, Japan). Deviation from HWE was tested using the χ^2 test for goodness-of-fit using SNPAlyze 5.1.1 Pro software (DYNACOM, Yokohama, Japan). Multiple linear regression analysis was performed to compare intellectual ability among rs2952768 SNP genotypes (the number of major alleles: 0, 1, or 2) using PASW software. Intellectual ability may be influenced by sex and years of education, and these variables were corrected for as covariates. We did not include age as a covariate because IQ score was already corrected for age. All p values were two tailed, and statistical significance was defined as $p < 0.05$.

Results

Influence of the rs2952768 genotype on current intellectual ability

Demographic variables, mean age, sex, and years of education are shown in Table 1. The mean age and years of education did not differ significantly between the genotype groups ($p > 0.59$), whereas the sex ratio differed significantly between groups ($p = 0.015$). We examined the possible effect of the rs2952768 genotype on intellectual ability. A significant effect of the SNP genotype was observed on current IQ ($\beta = -2.27$, $p = 0.026$). The number of C allele was correlated with higher IQ scores (Figure 1).

	Total	C/C	T/C	T/T	
Variables	(N = 298)	(N = 45)	(N = 123)	(N = 130)	p (H)
Age (years)	36.8 ± 12.4	36.3 ± 13.6	37.0 ± 11.7	36.8 ± 12.6	0.83 (0.38)
Sex (male/female)	122/176	11/34	60/63	51/79	**0.015 (8.35)**[a]
Education (years)	14.9 ± 2.3	15.0 ± 2.3	14.8 ± 2.3	15.0 ± 2.3	0.59 (1.06)

Means ± SD are shown. $p < 0.05$ is in boldface and underlined [a]χ^2 test.

Table 1: Demographic variables for subjects included in this study.

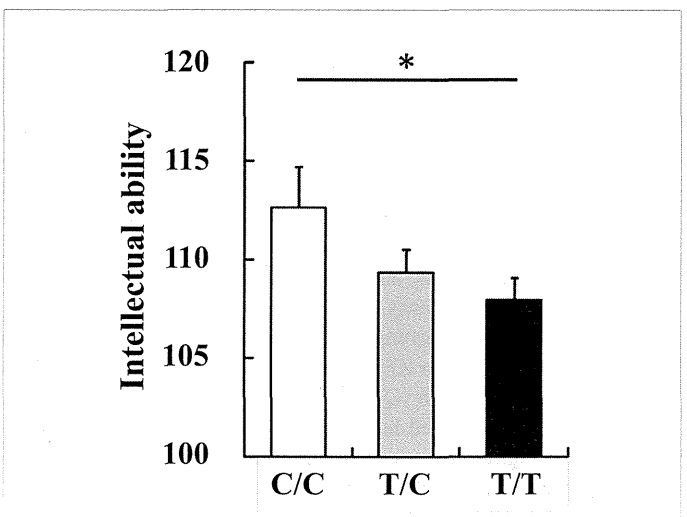

Figure 1: Impact of the rs2952768 genotype on intellectual ability
White, gray, and black bars represent individuals with the C/C genotype, T/C genotype, and T/T genotype, respectively. Error bars represent the standard error. The asterisk indicates $p<0.05$.

Discussion

We conducted an association study between verbal IQ and the rs2952768 SNP, which was recently identified as a potent SNP associated with opioid sensitivity that affects both the efficacy of opioid analgesics and liability to severe substance dependence. A significant effect of the SNP genotype was observed on current IQ (β = -2.27, p = 0.026), and the number of non-risk major C allele for severe drug and alcohol dependence was correlated with higher IQ scores (Figure 1), suggesting that the rs2952768 SNP is one of the genetic factors that contribute to human intellectual ability.

Several previous reports suggested associations between IQ score and addictive behaviors or the use of addictive substances, but the trend toward an association is not straightforward or easily understood [8-13]. Several reports indicated that people with lower IQ scores are more likely to become cigarette smokers [8,9]. Another report found that higher estimated IQ was significantly related to a shorter duration of opioid addiction [13]. High childhood IQ generally has been linked with alcohol dependence and more frequent alcohol consumption, and a 1 SD (15-point) increase in IQ score was found to be associated with an increased risk of illegal drug use in women, such as the use of cannabis, cocaine, amphetamines, amyl nitrate, and "magic mushrooms" [11,12]. The outcome in the present study that the number of non-risk major C allele for substance dependence in the rs2952768 SNP was correlated with higher IQ scores (Figure 1) is seemingly consistent with the results reported by Chastain et al. [13]. Although the rs2952768 SNP was identified as an opioid sensitivity-related SNP, the association was also found in the same direction with the severity of substance dependence, including alcohol dependence, methamphetamine dependence, and eating disorder [14]. Much more studies will be required to make definitive conclusions about the correlations or causal associations between IQ and the use of various addictive substances and vulnerability to or severity of dependence, since the fundamentally important pre-condition, the relationship of rs2952768 with severe drug dependence, has not been well-established.

In our previous study, the homozygote of the non-risk C allele for severe drug and alcohol dependence of the rs2952768 SNP was significantly associated with the elevated expression of a neighboring gene, cyclic adenosine monophosphate response element binding protein 1 (*CREB1*), which encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. CREB plays various roles as a transcription factor in many cells, including neuronal cells, and it is also involved in the molecular mechanisms that couple synaptic activity to long-term changes in neuronal plasticity, which is thought to underlie learning and memory [17]. Therefore, the elevated expression of the *CREB1* gene may promote the transcription levels of some target genes related to both human intellectual ability and addiction, leading to alterations in the neural mechanisms that are involved in both increasing intelligence and decreasing the rewarding effects of addictive substances. However, such speculative statements should be avoided before much more extensive studies are conducted in the future, and the precise mechanism by which elevated *CREB1* expression generally affects human opioid sensitivity requires further study.

The *CREB1* and *METTL21A* genes are both located within a linkage disequilibrium block that spans 2q33.3–2q34 [14]. Although these genes were not contained in the publicly available database that explores IQ-associated human genes [7], the chromosomal region 2q33 was included in the linkage regions, indicating that this region may be an IQ-associated region. Furthermore, chromosomal abnormalities, such as duplication and deletion of 2q33.3–2q34, were reported in patients with developmental delay and mental retardation [18,19], the severity of which may be related to IQ [20]. Despite the fact that the responsible genes within this region for IQ should be further clarified in future studies, these previous reports support the results of the present study, in which SNPs in this region may be associated with intellectual ability.

In conclusion, we identified a significant effect of the SNP genotype on current IQ, and the number of non-risk major C allele for drug and alcohol dependence was correlated with higher IQ scores. Although we should not over-interpret the present finding and the precise underlying mechanisms remain to be clarified in future studies, the results of the present study suggest that this SNP may be one of the genetic factors that contribute to human intellectual ability.

Acknowledgements

We acknowledge Mr. Michael Arends for his assistance with editing the manuscript. We thank all of the individuals who participated in this study. This work was supported by research grants from the Ministry of Health, Labour and Welfare (MHLW) of Japan (H22-seishin-ippan-001 and H25-Iyaku-020), MEXT/JSPS KAKENHI (grant no. 22390225, 23659565, 25116532, 20602020, 20390162, 23390377, 24790544, 24659549, and 22790518), CREST of JST, Japan Foundation for Neuroscience and Mental Health, and Smoking Research Foundation.

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Citation: Nishizawa D, Ohi K, Hashimoto R, Yamamori H, Yasuda Y, et al. (2014) Association between Genetic Polymorphism rs2952768, Close to the *METTL21A* and *CREB1* Genes, and Intellectual Ability in Healthy Subjects. J Addict Res Ther 5: 178. doi: 10.4172/2155-6105.1000178

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Factors that Affect Intravenous Patient-Controlled Analgesia for Postoperative Pain Following Orthognathic Surgery for Mandibular Prognathism

Yoshinori Aoki[1,2], Kaori Yoshida[1,2], Daisuke Nishizawa[1], Shinya Kasai[1], Tatsuya Ichinohe[2], Kazutaka Ikeda[1]*, Ken-ichi Fukuda[2]

1 Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, **2** Department of Dental Anesthesiology, Tokyo Dental College, Tokyo, Japan

Abstract

The predictors of postoperative pain and analgesic consumption were previously found to include preoperative pain, anxiety, age, type of surgery, and genotype, but remaining unclear was whether intraoperative factors could predict postoperative pain. In the present study, we investigated the time-course of fentanyl consumption using intravenous patient-controlled analgesia records from patients who underwent orthognathic surgery for mandibular prognathism and analyzed the influence of anesthesia methods and surgical methods together with sex on the time course. A significant difference in the time course of fentanyl administration was found ($P<0.001$). No significant difference in the time course of fentanyl administration was found between males and females ($P=0.653$), with no interaction between time course and sex ($P=0.567$). No significant difference in the time course of fentanyl administration was found among anesthesia methods, such as fentanyl induction followed by fentanyl maintenance, fentanyl induction followed by remifentanil maintenance, and remifentanil induction followed by remifentanil maintenance ($P=0.512$), but an interaction between time course and anesthesia method was observed ($P=0.004$). A significant difference in the time course of fentanyl administration was found between surgical methods, such as bilateral mandibular sagittal split ramus osteotomy (BSSRO) and BSSRO combined with Le Fort I osteotomy (bimaxillary; $P=0.008$), with no interaction between time course and surgical method ($P=0.535$). Total postoperative 24 h consumption associated with the bimaxillary procedure was significantly higher than with BSSRO ($P=0.008$). The present results indicate that administration patterns and total 24 h consumption were different among the three groups of anesthesia methods and between the two groups of surgical methods, respectively. Although more research on patient-controlled analgesia patterns and consumption is necessary, the present study will contribute to adequately relieving individual patients from postoperative pain.

Citation: Aoki Y, Yoshida K, Nishizawa D, Kasai S, Ichinohe T, et al. (2014) Factors that Affect Intravenous Patient-Controlled Analgesia for Postoperative Pain Following Orthognathic Surgery for Mandibular Prognathism. PLoS ONE 9(6): e98548. doi:10.1371/journal.pone.0098548

Editor: Ryota Hashimoto, United Graduate School of Child Development, Osaka University, Japan

Received January 22, 2014; **Accepted** May 5, 2014; **Published** June 3, 2014

Funding: This work was supported by grants from the Ministry of Health, Labour and Welfare (MHLW) of Japan (H21-3jigan-ippan-011, H22-Iyaku-015, and H25-Iyaku-020), JSPS KAKENHI grant no. 20602020, 20390162, 23390377, 24790544, 24659549, and 26293347, MEXT KAKENHI grant no. 25116532, the Smoking Research Foundation, the Naito Foundation, and the Astellas Foundation for Research on Metabolic Disorders. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Kazutaka Ikeda is a PLOS ONE Editorial Board member. This does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

* E-mail: ikeda-kz@igakuken.or.jp

Introduction

Every year, 234.2 million major surgical procedures are performed worldwide [1]. These patients experience postoperative pain, and the range of pain varies from mild to severe. Postoperative pain management is very important to reduce distress caused by pain itself, contribute to cardiovascular stability [2] and proper respiratory function [3], and enable early recovery [3]. Postoperative pain is frequently controlled by opioids, which are especially heavily used in the United States [4]. Postoperative pain is reportedly affected by preoperative pain, anxiety, age, and type of surgery, and postoperative analgesic consumption is affected by type of surgery, age, and psychological distress [5]. Clarification and the control of preoperative and intraoperative factors will provide patients with more effective pain management.

In the present study, we investigated the time course of fentanyl consumption using the intravenous patient-controlled analgesia (IV-PCA) records of patients who underwent orthognathic surgery for mandibular prognathism and analyzed the factors (e.g., sex, anesthesia method, and surgical method) that may influence postoperative pain management. We found that the time course of IV-PCA was associated with the anesthesia method (i.e., time course × anesthesia method interaction) and surgical method (i.e., main effect).

Materials and Methods

1. Patients

The study protocol was approved by the Institutional Review Boards of Tokyo Dental College and the Tokyo Metropolitan Institute of Medical Science. Written informed consent was obtained from all of the patients and from parents if the patient was under 20 years old. Enrolled in the study were 143 healthy patients (American Society of Anesthesiologists Physical Status I

[ASA PS I], 15–53 years old, 56 males and 87 females) who were scheduled to undergo orthognathic surgery for mandibular prognathism at Tokyo Dental College Suidobashi Hospital. Patients were excluded preoperatively if they had a history of acute or chronic kidney injury, drug abuse, or chronic pain or were unable to use the IV-PCA device.

2. Anesthesia

The groups comprised consecutive patients who underwent cosmetic orthognathic surgery for mandibular prognathism and received fentanyl induction and maintenance (F-F group) over a half-year period prior to 2010, consecutive patients who underwent the same surgery and received fentanyl induction and remifentanil maintenance (F-R group) in the first half of 2010, and consecutive patients who underwent the same surgery and received remifentanil induction and maintenance (R-R group) in the second half of the year 2010. All of the groups were orally premedicated with 5 mg diazepam and 150 mg famotidine 90 min before the induction of anesthesia.

In the F-F group, the patients were inducted with 2 μg/kg fentanyl. General anesthesia was performed with propofol at a target blood concentration of 4–6 μg/ml using a target-controlled infusion (TCI) pump (TE-317, Terumo, Tokyo, Japan). Vecuronium (0.1 mg/kg) was administered to facilitate nasotracheal intubation (Portex; inner diameter, 6.5–8.0 mm; Smiths Medical Japan, Tokyo, Japan) and maintained at 0.08 mg/kg/h during surgery. Whenever systolic blood pressure or heart rate increased more than 20% over baseline during surgery, fentanyl was intravenously administered at 1 μg/kg.

In the F-R group, the patients were inducted with 2 μg/kg fentanyl. General anesthesia was performed with propofol at a target blood concentration of 4–6 μg/ml using a TCI pump. Recuronium (0.6 mg/kg) was administered to facilitate nasotracheal intubation (Portex; inner diameter, 6.5–8.0 mm; Smiths Medical Japan, Tokyo, Japan) (Portex; inner diameter, 6.5–8.0 mm; Smiths Medical Japan, Tokyo, Japan). General anesthesia was maintained with 0.125–0.5 μg/kg/min remifentanil and 7 μg/kg/min recuronium during surgery. The patients received 100 μg fentanyl as a transitional opioid at the end of surgery.

In the R-R group, the patients were inducted with 0.5 μg/kg/min remifentanil. General anesthesia was performed with propofol at a target blood concentration of 4–6 μg/ml using a TCI pump. Recuronium (0.6 mg/kg) was administered to facilitate nasotracheal intubation (Portex; inner diameter, 6.5–8.0 mm; Smiths Medical Japan, Tokyo, Japan). General anesthesia was maintained with 0.125–0.5 μg/kg/min remifentanil and 7 μg/kg/min recuronium during surgery. The patients received 100 μg fentanyl as a transitional opioid at the end of surgery.

In the three groups, the lungs were ventilated with oxygen-enriched air. All of the patients received local anesthesia at the surgical sites with 8 ml of 2% lidocaine that contained 12.5 μg/ml epinephrine.

3. Surgery

Sagittal split osteotomy described by Obwegeser [6] is likely the most frequently used procedure for osteotomy to correct mandibular anomalies, including hypoplasia, hyperplasia, and asymmetries. Le Fort I osteotomy, first described by Wassmund [7] and later standardized by Obwegeser [8] and Bell [9], has also become the most frequently used procedure for osteotomy in the maxilla [10]. In the present study, the surgical methods for mandibular prognathism included bilateral mandibular sagittal split ramus osteotomy (BSSRO) and BSSRO combined with Le Fort I osteotomy (bimaxillary). Bimaxillary surgery was performed for patients who had been deemed to present only marginal improvements in mandibular prognathism after BSSRO alone.

4. Postoperative pain management

At the end of surgery, 50 mg rectal diclofenac sodium and 8 mg intravenous dexamethasone were administered to prevent postoperative orofacial edema/swelling. After emergence from anesthesia and tracheal extubation, 1.25 mg droperidol was intravenously administered to prevent nausea/vomiting, and IV-PCA with 20 μg/ml fentanyl commenced using a CADD-Legacy PCA pump (Smiths Medical Japan, Tokyo, Japan). Droperidol (0.1 mg/ml) was co-administered with fentanyl to prevent nausea/vomiting because of a high incidence (up to 30%) of nausea/vomiting with PCA fentanyl in young females [11]. A bolus dose of fentanyl of 20 μg on demand and a lockout time of 10 min were set. Continuous background infusion was not employed. Patient-controlled analgesia was continued for 24 h postoperatively. In the case of refractory adverse effects or inadequate analgesia, PCA with fentanyl was discontinued, and 50 mg rectal diclofenac sodium was prescribed as a rescue analgesic as required.

The PCA pump recorded all of the administration events, providing the researchers with the administration times, number of administrations, dose of the administrations, and number of attempts without administration. The number of administrations was converted to consumption every 2 h after the end of anesthesia. Consumption every 2 h was standardized by body weight. Total postoperative 24 h consumption was calculated as the sum of consumption every 2 h. In 63 of the 143 cases, the intensity of spontaneous pain was assessed 3 and 24 h postoperatively using a 100 mm visual analog scale (VAS), with 0 mm indicating no pain and 100 mm indicating the worst pain imaginable.

5. Statistical analysis

All of the data are expressed as mean ± SD or median (range) and were statistically analyzed using SPSS 19.0 software (SPSS, Chicago, IL, USA). Differences between groups and within time courses were assessed using mixed-design analysis of variance (ANOVA; one-way for independent groups and repeated measures with Huynh-Feldt correction). When a significant overall effect was detected, Bonferroni's test and Scheffe's test were used to compare the mean values of the groups and time courses, respectively. Differences between groups in total postoperative 24 h consumption were analyzed using one-way ANOVA. The threshold for statistical significance was $P<0.05$. The sample size for the present data was higher than the estimated size that possesses statistical power (1 minus type II error probability) of 98% for the Cohen's conventional "medium" effect size of 0.3. Power analyses were performed using G*Power v.3.1.5 [12].

Results

The attributes of the patients are shown in Table 1.

1. Sex

A significant difference was found in the time course of fentanyl administration ($F_{6.435,907.356}=24.211$, $MSe=0.166$, $P<0.001$, Huynh-Feldt). In the time course, 2 h consumption significantly decreased from 6 h to 24 h after the end of anesthesia compared with consumption in the first 2 h (Fig. 1). No significant difference was found in fentanyl administration between males and females ($F_{1,141}=0.204$, $MSe=0.593$, $P=0.653$, Huynh-Feldt), with no time course × sex interaction ($F_{6.435,907.356}=0.814$, $MSe=0.166$, $P=0.567$, Huynh-Feldt). No significant difference was found in

Table 1. Number of patients, age, sex, anesthesia methods, and surgical methods.

Sex	*n*, Age: median (range)	Anesthesia	*n*, Age: median (range)	Surgery	*n*, Age: median (range)
Male	56, 22.5 (16–53) years	F-F	44, 25.5 (16–53) years	BSSRO	94, 23.0 (15–49) years
		F-R	40, 22.0 (15–47) years		
Female	87, 25.0 (15–50) years			Bimaxillary	49, 25.0 (16–53) years
		R-R	59, 25.0 (16–50) years		
Total	143, 25.0 (15–53) years	Total	143, 25.0 (15–53) years	Total	143, 25.0 (15–53) years

doi:10.1371/journal.pone.0098548.t001

total postoperative 24 h consumption between males and females (Table 2; $F_{1,141} = 0.204$, $MSe = 7.115$, $P = 0.653$).

2. Anesthesia methods

A significant difference was found in the time course of fentanyl administration ($F_{6.661,932.489} = 24.653$, $MSe = 0.157$, $P<0.001$, Huynh-Feldt). In the time course, 2 h consumption significantly decreased from 6 h to 24 h after the end of anesthesia compared with consumption in the first 2 h (Fig. 2). No significant difference was found in fentanyl administration among the anesthesia methods ($F_{2,140} = 0.672$, $MSe = 0.592$, $P = 0.512$, Huynh-Feldt), but a significant time course × anesthesia method interaction was observed ($F_{13.321,932.489} = 2.359$, $MSe = 0.157$, $P = 0.004$, Huynh-Feldt). Consumption in the first 2 h in the R-R group was significantly higher than in the F-F group, but 8 h consumption in the R-R and F-R groups was significantly lower than in the F-F group. Nevertheless, total postoperative 24 h consumption was not significantly different among the three groups (Table 2; $F_{2,141} = 0.672$, $MSe = 7.108$, $P = 0.512$).

3. Surgical methods

A significant difference was found in the time course of fentanyl administration ($F_{6.482,913.936} = 24.144$, $MSe = 0.165$, $P<0.001$, Huynh-Feldt). In the time course, 2 h consumption significantly decreased from 4 h to 24 h after the end of anesthesia compared with consumption in the first 2 h. A significant difference was found in fentanyl administration between the surgical methods

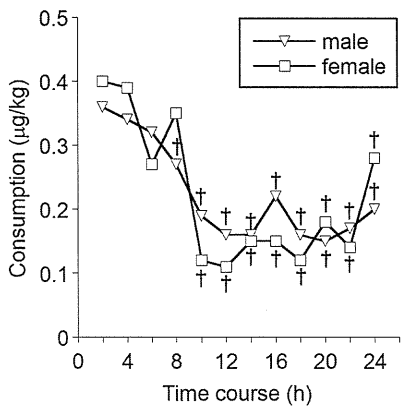

Figure 1. Differences in the time course of fentanyl administration between males and females. Main effects, interactions, and differences within time courses were analyzed using mixed-design ANOVA (one-way for independent groups and repeated-measures with Huynh-Feldt correction). The values indicate the medians. †$P<0.05$, compared with fentanyl consumption in the first 2 h.
doi:10.1371/journal.pone.0098548.g001

($F_{1,141} = 7.237$, $MSe = 0.565$, $P = 0.008$, Huynh-Feldt), but no time course × surgical method interaction was observed ($F_{6.482,913.936} = 0.855$, $MSe = 0.165$, $P = 0.535$, Huynh-Feldt). Consumption in the first 2 h was higher in the bimaxillary group than in the BSSRO group (Fig. 3). Total postoperative 24 h consumption in the bimaxillary group was significantly higher than in the BSSRO group (Table 2; $F_{1,141} = 7.237$, $MSe = 6.778$, $P = 0.008$, Huynh-Feldt).

4. Visual analog scale

The attributes of the patients are shown in Table S1. No significant difference was found in VAS scores between the anesthesia methods (F-F and F-R groups) at 3 h ($t_{61} = -0.713$, $P = 0.478$) and 24 h ($t_{61} = -0.098$, $P = 0.992$). A significant positive correlation was found between total postoperative 24 h consumption and VAS scores at 3 h, but the correlation coefficient was relatively small ($r = 0.295$, $P = 0.019$). No significant positive correlation was found between total postoperative 24 h consumption and VAS scores at 24 h ($r = 0.240$, $P = 0.058$). A significant positive correlation was found between VAS scores at 3 and 24 h, and the correlation coefficient was relatively large ($r = 0.667$, $P<0.001$).

Discussion

The predictors of postoperative pain were previously found to include preoperative pain, anxiety, age, type of surgery [5], and genotype [11,13–15]. We investigated orthognathic patients in whom these predictive factors are considered to be relatively similar. They had been treated by a few orthodontists in the hospital over several years. Their anxiety appeared to be much less than patients who presented in the emergency room. Almost all of the patients were young (mean age = 23.16 years, SD = 0.696 years) and healthy (ASA PS I). Orthognathic surgery was performed after body growth ceased. Orthognathic procedures, such as BSSRO and BSSRO combined with Le Fort I osteotomy, have been well established. The patients were subjected to uniform invasiveness by these typical operations. Postoperative pain after BSSRO has been reported to be more intense than after soft tissue surgery [16]. Thus, these patients had no preoperative pain (e.g., inflammatory pain), had less anxiety, were young, and had similar levels postoperative pain; therefore, they were deemed to be suitable for inclusion as subjects to investigate the factors that influence the time course of IV-PCA.

Young patients were reported to be more sensitive to postoperative pain than older patients [5]. We did not analyze the association between age and postoperative fentanyl consumption because our data were collected mainly from young patients.

Generally, sex is not associated with postoperative pain [5], although postoperative pain in patients who underwent impacted third molar extraction was associated with sex [17]. Pain assessed

Table 2. Total postoperative 24 h consumption.

Subjects	*n*	Total 24 h consumption (μg/kg)	
		median	range
Sex			
Male	56	2.88	0.00–10.00
Female	87	2.40	0.00–11.34
Total	143	2.59	0.00–11.34
Anesthesia method			
F-F	44	2.64	0.00–10.54
F-R	40	2.28	0.00–9.07
R-R	59	2.70	0.00–11.34
Total	143	2.59	0.00–11.34
Surgical method			
BSSRO	94	2.29	0.00–9.07
Bimaxillary	49	3.16*	0.00–11.34
Total	143	2.59	0.00–11.34

*$p<0.05$, significant difference between BSSRO and bimaxillary groups.
doi:10.1371/journal.pone.0098548.t002

by a visual analog scale (VAS) during the first 24 h in females was significantly higher than in males, but the VAS score after the first 24 h was not significantly different between males and females [17]. The initially higher level of pain in females may be attributable to a smaller and thinner mandible in females [17]. The surgical site in the present study was similar to impacted third molar extraction; thus, we analyzed the association between sex and postoperative fentanyl consumption. However, our data did not show a significant difference in fentanyl consumption between males and females. Impacted third molar extraction might cause more micro-bone fractures in females than in males. Because osteotomy is not a micro-bone fracture but rather an artificial fracture, postoperative fentanyl consumption might not have been affected by sex differences in the structure of the mandible in the present study.

Anesthesia methods were analyzed by two-way ANOVA without sex as a covariate because no significant difference was found between males and females in the present study. A time course × anesthesia method interaction was observed, in which consumption in the first 2 h was higher than 4 h consumption in the R-R and F-R groups, but 2 h consumption was lower than 4 h consumption in the F-F group. The context-sensitive half-life of remifentanil is extremely less than fentanyl [18]. The recovery of psychomotor function after total intravenous anesthesia (TIVA) with remifentanil, which does not use any inhalational agents, was 30–120 min faster than TIVA with fentanyl [19]. Orthognathic patients who were maintained with TIVA with remifentanil had

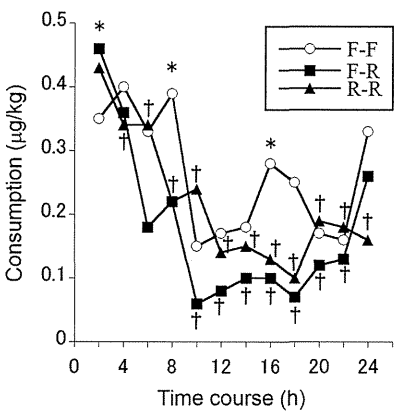

Figure 2. Differences in the time course of fentanyl administration among anesthesia methods. Main effects, interactions, and differences within time courses were analyzed using mixed-design ANOVA (one-way for independent groups and repeated-measures with Huynh-Feldt correction). F-F, fentanyl induction followed by fentanyl maintenance; F-R, fentanyl induction followed by remifentanil maintenance; R-R, remifentanil induction followed by remifentanil maintenance. The values indicate the medians. †$P<0.05$, compared with fentanyl consumption in the first 2 h; *$P<0.05$, significant difference among the three groups in 2 h fentanyl consumption.
doi:10.1371/journal.pone.0098548.g002

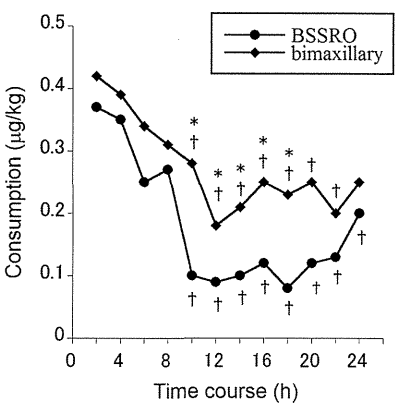

Figure 3. Differences in the time course of fentanyl administration between surgical methods. Main effects, interactions, and differences within time courses were analyzed using mixed-design ANOVA (one-way for independent groups and repeated-measures with Huynh-Feldt correction). The values indicate the medians. †$P<0.05$, compared with fentanyl consumption in the first 2 h; *$P<0.05$, significant difference between the BSSRO and bimaxillary groups.
doi:10.1371/journal.pone.0098548.g003

significantly higher pain scores within the first 4 h postoperatively [20]. Thus, the groups that were maintained with remifentanil (i.e., the F-R and R-R groups) may recognize postoperative pain father than the group that was maintained with fentanyl (i.e., the F-F group). Faster psychomotor recovery and the faster recognition of pain might explain why the groups that were maintained with remifentanil had higher fentanyl consumption in the first 2 h than the group that was maintained with fentanyl. Interestingly, the administration pattern was different between the remifentanil and fentanyl groups, but total postoperative 24 h consumption was not different among the three groups of anesthesia methods. Additionally, the 3 and 24 h VAS scores were mostly less than 50 mm and not different between anesthesia methods (F-F and F-R groups), indicating that subjective pain was appropriately controlled in both the F-F and F-R groups.

We had empirically known that bimaxillary surgery is experimentally more painful than BSSRO. Postoperative pain following BSSRO and Le Fort I osteotomy is conveyed from the surgical sites to supraspinal sites by the third and second branches of the trigeminal nerve, respectively. Thus, postoperative pain following bimaxillary surgery was conveyed from the surgical sites to supraspinal sites by both the second and third branches of the trigeminal nerve. Our results suggest that postoperative pain increased because of the increase in the number of branches of the trigeminal nerve from the surgical site. Further studies of single Le Fort I osteotomy (second branch of the trigeminal nerve) are required to determine whether the increase in postoperative pain is caused by synergistic or additive effects.

The present study involved healthy patients who underwent oral surgery. The influence of perioperative factors on IV-PCA was controlled. The results showed that the administration patterns and total 24 h consumption were different among the three groups of anesthesia methods and between the two groups of surgical methods, respectively. Although more research on patient-controlled analgesia patterns and consumption is necessary, the present study will contribute to adequately relieving individual patients from postoperative pain.

Supporting Information

Table S1 Frequency of patients and VAS scores.
(DOCX)

Acknowledgments

We thank Mr. Michael Arends for his assistance with editing the manuscript. We are grateful to the volunteers for their participation in this study and the anesthesiologists and surgeons at Tokyo Dental College, Tokyo, Japan.

Author Contributions

Conceived and designed the experiments: YA KI KF. Performed the experiments: YA KY DN SK. Analyzed the data: YA DN. Contributed reagents/materials/analysis tools: KY TI KI KF. Wrote the paper: YA DN KI KF.

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—Original—

Stress Sensitivity in Patients with Atopic Dermatitis in Relation to the Translocator Protein 18 kDa (TSPO)

Mio Kaga[1,2], Yurie Nakamoto[2], Kazuhiko Nakamura[3], Kazutaka Ikeda[2], Mitsunobu Yoshii[2] and Seiji Kawana[1]

[1]Department of Dermatology, Nippon Medical School
[2]Tokyo Metropolitan Institute of Medical Science
[3]Department of Neuropsychiatry, Hirosaki University School of Medicine

Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease, characterized by pruritic and eczematous skin lesions and dermatitis that worsens under stressful conditions. However, the relation of these symptoms to an individual's stress sensitivity is not well understood. On the other hand, expression of the translocator protein (18 kDa) (TSPO), formerly known as the peripheral-type benzodiazepine receptor, has been used as a biological marker of trait anxiety and stress sensitivity. The present study was designed to address this issue by examining TSPO in patients with AD. Fifty-two patients with AD (30 male and 22 female) and 163 healthy volunteers (89 male and 74 female) participated in this study. State-Trait Anxiety Inventory (STAI) scores were significantly higher in patients with AD, especially male patients, than in healthy subjects. The expression of platelet TSPO, as determined with a binding assay with [^{3}H] PK11195, was also significantly higher in patients with AD, indicating that AD is a stress-responsive disease. In genomic analysis using lymphocytes, a single-nucleotide polymorphism of the human TSPO gene at exon 4 (485G>A), which is presumably associated with an individual's stress sensitivity, showed significantly lower frequencies of G/G and higher frequencies of G/A in patients with AD than in healthy subjects. The severity of AD, as determined with the Scoring of Atopic Dermatitis index, was correlated with TSPO expression in male patients with the G/A phenotype. In conclusion, the present study provides new evidence that variation in the TSPO gene affects susceptibility to AD.
(J Nippon Med Sch 2014; 81: 148–156)

Key words: atopic dermatitis, stress sensitivity, translocator protein 18 kDa (TSPO), genomic analysis

Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease of persons with the predisposing factor of atopy. In 2006, mutations in the gene for the production of filaggrin were found to strongly increase the risk of AD[1]. Genetic

Correspondence to Mitsunobu Yoshii, MD, PhD, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kami-kitazawa, Setagaya-ku, Tokyo 156-8506, Japan
E-mail: yoshii-mt@igakuken.or.jp
Journal Website (http://www.nms.ac.jp/jnms/)

mutations in filaggrin often reduce the barrier function of skin, elevate immunoglobulin E levels, and lead to the pathogenesis of chronic dermatitis[2].

Many patients with AD live under stressful conditions, in which intense unavoidable itching disturbs their sleep and markedly reduces their quality of life[3]. Repeated scratching can cause erythema, pigmentation, and lichenification. Due to these cosmetic problems, the patients are exposed to psychological stress as well as physical stress. Frequent scratching as a means of escaping the intolerable stress worsens the pruritic and eczematous skin lesions.

AD can lead to psychological disturbances, such as stigmatization, social isolation, and discrimination[4]. Patients with AD have been reported to exhibit anxiety, depression, and emotional excitability[5,6]. Psychological stress and symptoms of AD appear to form a vicious cycle[7]. It remains unclear, however, how stress affects AD.

On the other hand, there has been a growing interest in *the translocator protein (18 kDa)* (TSPO), formerly known as *the peripheral-type benzodiazepine receptor (PBR)*, in the subjects of steroidogenesis, apoptosis, and immunomodulation[8–10]. The TSPO is involved in the regulation of several major stress systems, *i.e.*, the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, the renin-angiotensin axis, and the neuroendocrine-immune axis[8].

Our previous studies have found that the expression of TSPO on platelets is significantly correlated with the trait anxiety score in healthy human subjects[11]. The evidence for TSPO as a promising biological marker of stress has prompted us to investigate the stress response of TSPO at the genomic level.

A 485G>A single nucleotide polymorphism (SNP) in a coding region of exon 4 of the TSPO gene was found to affect susceptibility to panic disorder (PD)[12]. Before the onset of PD, individuals with the G/G genotype showed high anxiety sensitivity and an increase in TSPO. Our study suggests that individuals with the G/G genotype are at increased risk for stress-related disorders.

The present study was designed to examine how the symptoms of AD are related to individual's stress sensitivities by analyzing the density of platelet TSPO together with the genetic variation of TSPO.

Materials and Methods

Subjects

Fifty-two patients with AD (30 male and 22 female) and 163 healthy volunteers (89 males and 74 female) participated in this study. The participants were given the State-Trait Anxiety Inventory (STAI), a self-reported measure of anxiety. For patients with AD, the Scoring of Atopic Dermatitis (SCORAD) index was performed. The SCORAD index is a well-established severity-scoring tool for AD which is widely used in dermatology. The SCORAD index consists of the interpretation of the extent of the disorder (A: according to the rule of nines; score 0–20), the intensity composed of 6 items (B: erythema, edema/papules, effect of scratching, oozing/crust formation, lichenification and dryness; score 0–63; each item has 4 grades: 0, 1, 2, and 3), and symptoms (C: itch, sleeplessness; score 0–20). All subjects were fully informed about the nature of the study and gave their written consent. This study was approved by the Ethics Committees of Nippon Medical School and Tokyo Metropolitan Institute of Medical Science.

Preparation of Platelet Membranes

Blood samples (20 mL) were collected, and platelets were isolated with our standard procedures[11]. In brief, blood samples (20 mL) were obtained from the subjects in the morning between 9:00 a.m. and 10:00 a.m. The samples were collected in plastic-walled, evacuated blood collection tubes (Venoject II, Terumo Corp., Tokyo, Japan) and spun twice at 180 x *g* for 15 minutes at 4℃. Platelet-rich plasma was collected and spun at 1,500 x *g* for 15 minutes at 4℃. The platelet-containing pellet was frozen at −80℃.

Before the binding assay, the samples were thawed, and each pellet was homogenized in 10 mL of ice-cold Tris-HCl buffer (50 mM, pH 7.4) in a homogenizer (Polytron PT-10, Thermo Fisher

Scientific, Inc., Waltham, MA, USA). The homogenate was then centrifuged at 49,000 x *g* for 15 minutes at 4℃, and the pellet was suspended in 100 volumes of Tris-HCl buffer.

The platelet membranes were finally adjusted to 0.1 mg protein/mL with assay buffer (50 mM Tris-HCl, pH 7.4). The protein content was determined with the Lowry technique.

Binding Assay

The binding of [^{3}H] PK 11195, a specific ligand of TSPO, to platelets was assayed with a method described previously[13]. Tissue (0.8 mL, 0.08 mg protein) was incubated with a radioligand (0.1 mL) and a cold ligand (or assay buffer; 0.1 mL) in an incubation volume of 1 mL (0℃–4℃) for 60 minutes. The reaction was terminated by rapid filtration over GF/B glass microfiber filters (FP-100, Whatman, GE Healthcare, Little Chalfont, UK) that had been soaked in poly-L-lysine solution (Sigma-Aldrich, St. Louis, MO, USA) using a cell harvester (M-24, Brandel, Gaithersburg, MD, USA), with 5 washes with 5 mL of ice-cold buffer.

The specific binding of [^{3}H] PK 11195 was defined as the difference in binding obtained in the presence and the absence of PK 11195 (10 μM, Research Biochemicals International, Natick, MA, USA). The radioactivity retained by the filters placed in a 24-well microplate (PicoPlate-24, PerkinElmer, Inc., Waltham, MA, USA) was measured with a microplate scintillation counter (Top Count, Packard Instrument Co., Meriden, CT, USA), using 500 μL of a scintillant (MicroScint-20, Packard Instrument Co.). [^{3}H] PK 11195 (86.0 Ci/mmol) was purchased from Daiichi Pure Chemical Company (Tokyo, Japan).

The dissociation constant (Kd) and the receptor density (Bmax) were determined with least-squares regression. Unless otherwise stated, the statistical data are presented as the mean and S.D.

Genomic Analysis

The 485G>A polymorphism of the TSPO gene was examined as described previously[12]. Genomic DNA was prepared from peripheral blood lymphocytes with a DNA extraction kit (Stratagene, La Jolla, CA, USA). The fragments including exon 4 of the TSPO gene were amplified with the polymerase chain reaction (PCR), and direct sequencing was performed. Sequence variations of the TSPO gene were analyzed within exon 4.

The PCR amplifications were performed in a 20-mL reaction mixture containing 100 ng of genomic DNA, 15 pM of each primer, 1.5 mM of $MgCl_2$, and 1 U Ex Taq polymerase (Takara, Tokyo, Japan).

The coding region in exon 4 of the TSPO gene was screened with direct sequencing, using the primer sets. Sequencing was performed on both strands with a sequencing kit (Big Dye Terminator Cycle Sequencing Kit, Applied Biosystems, Foster City, CA, USA) and a sequencer (ABI 3700, Applied Biosystems).

The SNPs were scored with custom genotyping products (TaqMan Assays-by-Design SNP Genotyping Service, Applied Biosystems) based on the TaqMan assay method[14]. Genotypes were determined with a sequence detection system instrument (ABI 7900, Applied Biosystems) and analysis software (SDS v2.0, Applied Biosystems).

Statistical Analysis

Pearson product-moment correlation and analysis of variance were used to identify associations among Bmax values and STAI scores. The allelic distributions were compared between patients and control subjects by means of chi-square statistics and Fisher's exact test. All differences were considered significant at $p<0.05$. Statistical analysis was performed with the Prism software program (version 4.0) for Macintosh (GraphPad Software, San Diego, CA, USA).

Results

The subjects were 52 patients with AD (30 male and 22 female) and 163 healthy volunteers (89 male and 74 female). The STAI scores were significantly higher in patients with AD, especially male patients, than in healthy subjects (**Fig. 1**). In male patients, both state and trait anxiety scores were significantly higher, whereas in female patients, only trait anxiety scores were significantly higher.

The expression of platelet TSPO, as determined

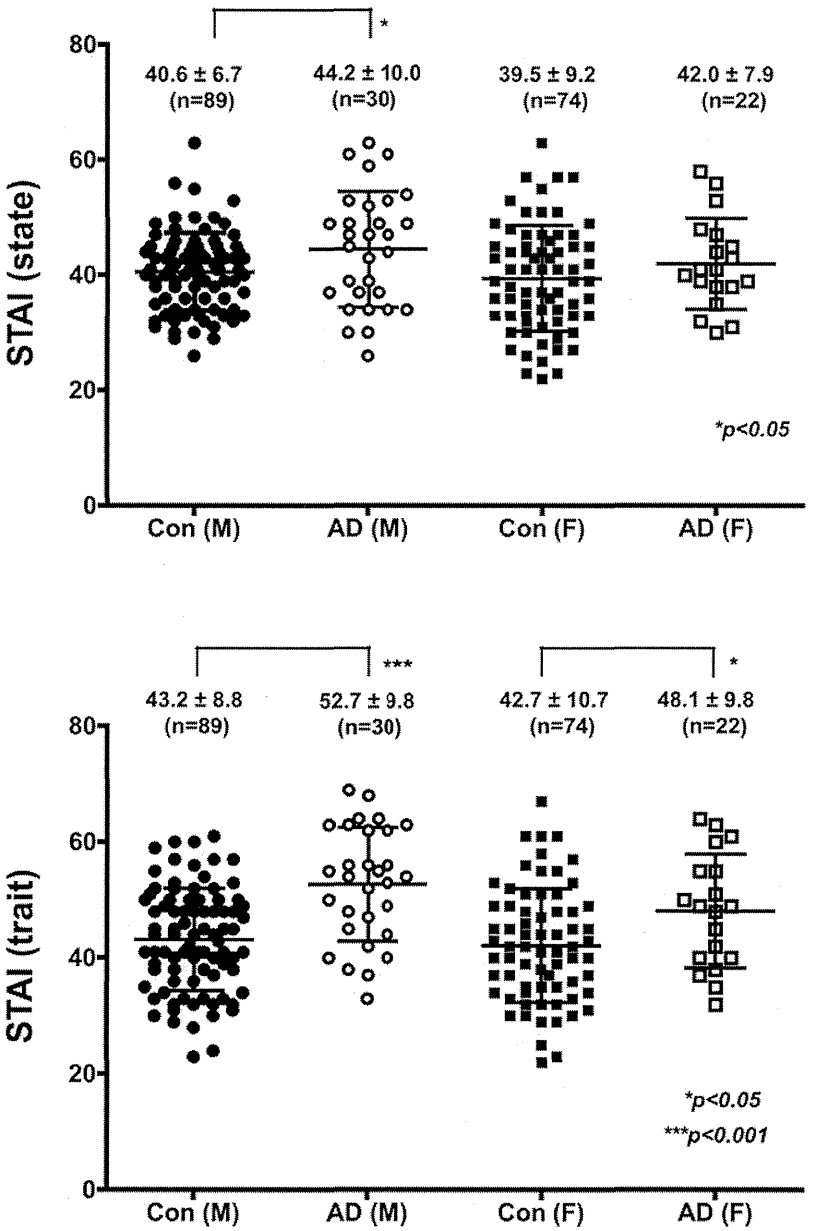

Fig. 1 Comparison of STAI scores of patients with atopic dermatitis and control subjects
Scores of the state anxiety (upper) and the trait anxiety (lower) are further compared between male (M) and female (F) subjects. There were significant differences in either state or trait anxiety between patients with atopic dermatitis (AD) and control subjects (Con), except for state anxiety in female subjects. The data are presented as means and S.D.

with a binding assay with [^{3}H] PK11195 in terms of Bmax, was also significantly higher in patients with AD than in healthy control subjects. The increase was greater in male patients (by 62% on average) than in female patients (by 22% on average).

Genomic analysis of the 485G>A polymorphism of the human TSPO gene in exon 4 showed, contrary to our expectation, that the G/G genotype was less frequent and the G/A and possibly A/A genotypes were more frequent in patients with AD than in control subjects (**Table 1**). The difference in the frequency distribution was significant in male