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IV. 研究成果の刊行物・別冊

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原　著

本邦における先天性高インスリン血症の実態調査

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要　旨

本邦における先天性高インスリン血症の実態を明らかにするため，平成21～22年度厚生労働省難治性疾患克服研究事業の研究班活動の一環として，全国疫学調査を行った．対象は2007年10月から2009年9月の2年間に出生した高インスリン血症の患児で，全国の300床以上の病院のうち小児科ないし新生児科をもつ1,057施設に調査票を送付し，624施設から回答を得た（回収率59.0%）．188人の患者発生を同定し，うち発症後3か月以内に治療が不要になった一過性高インスリン血症群が127人，持続性高インスリン血症群が61人で，出生数当たりの年間発症率は，一過性群で約17,000人に1人，持続性群で約35,400人に1人であった．低血糖時のインスリン/血糖比，総ケトン体，遊離脂肪酸は両群間で有意差を認めなかったが，在胎週数，出生体重のパーセンタイル値は有意に一過性群で低かった．ジアゾキサイドの副作用である乏尿・浮腫，うっ血性心不全は106人中25人（23.6%）に認めた．オクトレオチド使用児では22人中2人（9.1%）に壁在胆石を認めた．外科的治療は持続性群の61人中7人（11.5%）に施行された．神経学的予後については短期予後のみであるが，先天性高インスリン血症以外に明らかな原因のあるものを除外すると両群合わせて15人（8.0%）に何らかの神経学的後遺症を認めた．

キーワード：先天性高インスリン血症，全国疫学調査

はじめに

先天性高インスリン血症は，新生児期・乳児期に持続する低血糖症で発症する．稀な疾患であるが重篤な低血糖をきたした児には高頻度で神経学的後遺症を残すため[1)2)]，その適切な管理は臨床上極めて重要である．本症は，生後数か月以内に軽快する一過性のものと，それ以降も持続する持続性のものに大別される．一過性本症は母体糖尿病，母体薬剤投与や低酸素血症，胎児機能不全によるストレス誘発性のものなどが知られており，一般に非遺伝性であると考えられているが，高インスリン血症が起こる原因は明らかにされていない[3)]．一方持続性本症は，大部分が遺伝性と考えられている．既にいくつかの原因遺伝子が同定されており，代表的なものとして，膵β細胞のグルコース応答性インスリン分泌に重要なATP感受性カリウムチャネル（K_{ATP}チャネル）を構成するSUR1（*ABCC8*遺伝子），Kir 6.2（*KCNJ11*遺伝子）の異常によるものが最も多く，次いで高インスリン血症・高アンモニア血症症候群をきたすグルタミン酸脱水素酵素（*GLUD1*遺伝子）異常が多いとされている．K_{ATP}チャネル遺伝子異常による本症には，膵全体に病変が及ぶびまん性病変と，膵の一部に病変が局在する局所性病変，ないし極めて稀ではあるが局所性病変が複数存在する多発性病変が存在することが知られている．びまん性病変はK_{ATP}チャネル遺伝子の両アリル変異による劣性遺伝性の本症が多い．一方，局所性病変及び多発性病変は父由来の片アリル変異をもつ個体に，膵β細胞の体細胞レベルでの母由来アリルの欠失がおこることにより生じる．K_{ATP}チャネル遺伝子の近傍には母由来のアリルのみが転写されている腫瘍抑制遺伝子，*H19*や*CDKN1C*が存在しており，母由来アリル欠失により，K_{ATP}チャネル遺伝子機能と腫瘍抑制遺伝子機能が同時に失われるため，異常細胞の増殖がおこって局所性病変及び多発性病変を形成する．持続性高インスリン血症は，欧米では5万人に1人の発症頻度と報告されている[4)]．K_{ATP}チャネル遺伝子異常による劣性，局所性の本症には，K_{ATP}チャネルを開口させてインスリン分泌を抑制させるジアゾキサイドは効果がないとされている．従来，内科的治療に抵抗性の症例では神経学的後遺症を回避するために95%以上の膵亜全摘が行われてきたが，多くは治癒しないか，術後糖尿病に至っており[2)]，

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その予後は必ずしも芳しいものではなかった．近年になって，欧米を中心に持続性本症の分子遺伝学的理解が進み，治療方法に長足の進歩が見られるようになった[5)6)]が，本邦では保険適応の制限などとも関連して本症の診断・治療は大きく後れをとっており，その実態すら明らかではなかった．本研究では，先天性高インスリン血症の治療における状況改善の第一歩として我が国での発症実態，治療実態を明らかにすることを目的として全国疫学調査を行った．

対象および方法

全国の300床以上の病院のうち小児科ないし新生児科をもつ1,057施設に調査票を送付し，2007年10月から2009年9月の2年間に出生した高インスリン血症患児について調査を行った．過去の文献では，一過性本症は発症後治癒するまでに数週から数か月，長いと1年かかると報告されているが，3か月以上続くものは例外的長期例であるとされていることから[3)7)]，発症後3か月以内に一切の治療が不要になる症例を一過性，それ以後も治療継続が必要な症例を持続性と定義した．それぞれについて発症頻度，臨床データ，治療実態，予後について調査を行い，また両群を比較して，臨床的に両群を鑑別することが可能かどうかについても検討した．さらに治療薬による副作用発生状況についても調査した．

調査項目は，生年月，性別，在胎週数，出生体重，同胞数，合併症（自由記載），家族歴（自由記載），発症時年齢，低血糖時の血液検査データ（血糖，インスリン，総ケトン体（アセト酢酸，3-ヒドロキシ酪酸），遊離脂肪酸，乳酸，ピルビン酸）と，内科的治療に関しては，高濃度ブドウ糖輸液（投与の有無，糖注入率（GIR）の最高値），ステロイド（使用の有無），ジアゾキサイド・オクトレオチド・グルカゴン（使用の有無，有効性，最大投与量，投与期間，副作用の有無）とし，副作用有りの場合，ジアゾキサイド（乏尿・浮腫，うっ血性心不全，高尿酸血症，白血球減少症，その他を選択し，その他を選んだ場合自由記載），オクトレオチド（胆石・消化器症状・その他を選択し，その他を選んだ場合自由記載），グルカゴン（自由記載）とした．一過性症例にはApgar score 1分値・5分値，出生時赤芽球数，胎児機能不全の有無を，持続性症例には遺伝子検査の有無，外科的治療（有りの場合，手術時年齢，切除割合（%），病理所見（自由記載），術後の糖尿病発症の有無，術後の低血糖の残存の有無）を追加した．

発症頻度は，厚生労働省発表の人口動態調査の出生数より，平成20年度109万1,150人（確定値），平成21年度106万9,000人（推計値）を用いて計算した．また出生体重のパーセンタイル値は日本人在胎期間別出生時体格基準値の作成に関する研究[8)]から算出した．母集団の性質により2群間の平均値の差の検定はunpaired t検定あるいはMann-WhitneyのU検定を用いて行い，また発症頻度の群間比較にはχ^2検定を用い，$p<0.05$を有意とした．

結　果

調査票を送付した1,057施設中624施設から回答があり（59.0%），一過性高インスリン血症127人，持続性高インスリン血症61人を同定した．

①出生数当たりの年間発症率

一過性群で約17,000人に1人（127人/2,160,150人・2年），持続性群で約35,400人に1人（61人/2,160,150人・2年）であった．一過性本症が持続性本症のおよそ2倍の頻度で発症しており，持続性本症の発症頻度は欧米での報告より若干多かった．

②男女比

一過性群は男児86人（67.7%），女児39人（30.7%），記載なし2人で男児の占める割合が高かったが，持続性群では男児30人（49.0%），女児30人（49.0%），記載なし1人とほぼ男女同数であった．一過性群で持続性群より明らかに男児の比率が高かった．

③在胎週数，出生体重のパーセンタイル値

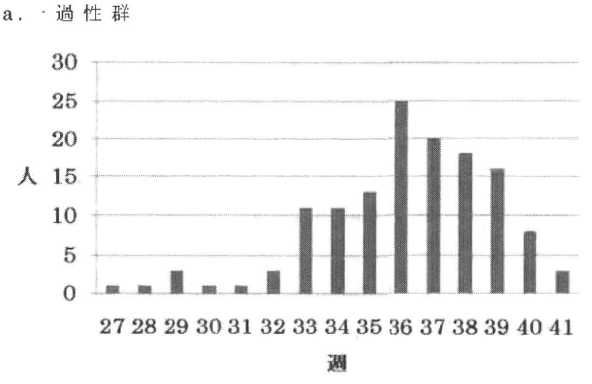
有意に一過性群で低く（在胎週数，出生体重ともp<0.01），母体や児の要因による早産，small for gestational age（SGA）症例が大部分を占めており，また胎児機能不全のみられた症例が多かった（46.5%）（図1，2）．

④発症時日齢

一過性群では早期新生児期（生後7日以内）発症が117人（92.1%）と大部分を占めており，晩期新生児期（生後1～4週）以降の発症が7人（5.5%）で，最年長は生後55日（在胎29週，776g出生の女児）の症例であった．持続性群では早期新生児期発症例が52人（85.2%）で，晩期新生児期以降の発症が9人（14.8%）みられ，最年長は生後7か月発症の2人（在胎40週，2,872g出生の男児と在胎39週，3,056g出生の男児）であった．生後遅発発症例は有意に持続性群に多かった（p<0.05）．

⑤その他の先天異常の合併

一過性群では15人（11.8%）に先天的な合併症を認め，その内訳は染色体異常5人（21トリソミー1人，モザイク型18トリソミー1人，13トリソミー2人，47，XXX 1人），2つ以上の奇形合併症例（心疾患，腎泌尿器疾患，耳介低形成などの外表奇形）3人，心疾患4人，多指・多趾症2人，内反足1人であった．重篤な合併症として，頭蓋内出血3人，心停止1人の報告があり，また染色体異常1人，多発奇形症例1人がそれぞれ生後39日，生後59日で死亡していた．持続性群



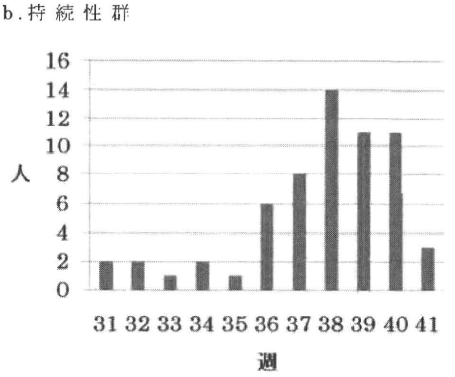
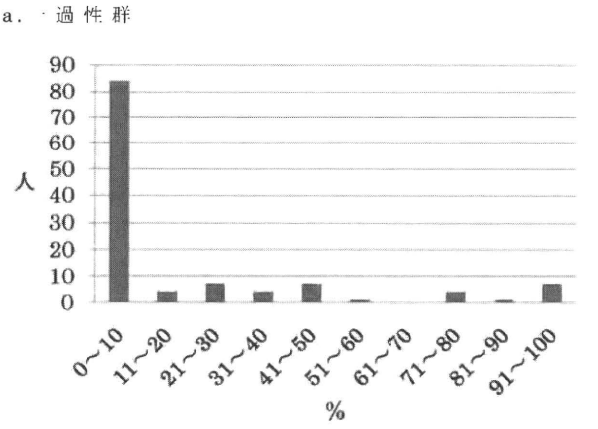


図1　在胎週数
在胎週数は一過性群で有意に短かった（p<0.01）.



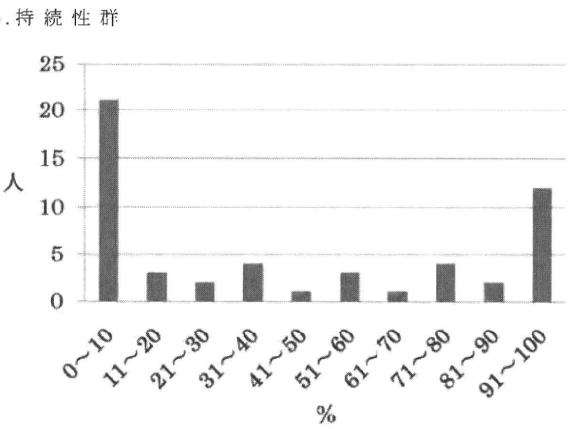


図2　出生体重のパーセンタイル値
出生体重のパーセンタイル値も有意に一過性で低値であった（p<0.01）.

では18人（29.5%）に合併を認め，染色体異常1人{46, XX, der (9) t (3 : 9) (q25.3 : p24)}，Beckwith-Wiedemann症候群1人，無脾症候群1人，2つ以上の奇形合併例6人（小脳低形成，心疾患，門脈欠損，横隔膜ヘルニア，食道裂孔ヘルニア，外表奇形など），心疾患4人，先天性小腸閉鎖1人，馬蹄腎＋水腎症1人，停留精巣1人，尿道下裂1人，顔面血管腫1人であった．また低酸素性虚血性脳症＋脳梗塞を1人に認めた．両者とも一般集団の胎児奇形の割合（約5%）より高く，また一過性群と持続性群では持続性群の方が有意に合併症を持つ割合が高かった（p<0.01）.

⑥低血糖時の臨床検査データ

インスリン/血糖比，総ケトン体，遊離脂肪酸（図3 A, B, C），ケトン体比（アセト酢酸/3-ヒドロキシ酪酸），乳酸/ピルビン酸比を一過性群と持続性群で比較したが，いずれも有意差はみられなかった(p>0.05).

⑦内科的治療

高濃度輸液はほとんどの患児に施行されていたが，一過性群{平均10.5mg/kg/分（3~25)}，持続性群{平均10.9mg/kg/分（1~22)}で両群のGIRの最高値に有意差はみられなかった(p>0.05)．ステロイドの使用頻度は一過性群，持続性群併せて36.4%であった．ジアゾキサイドの使用量，使用日数は図4のとおりで，使用量については両群に有意差を認めなかった（p>0.05)．オクトレオチドは一過性群の6人{平均8.0μg/kg/日（2.7~18)}，持続性群の14人{平均16.9μg/kg/日（2.5~30)}に使用されていた．グルカゴンが使用された症例も両群合わせて19人存在した．

⑧薬剤副作用

ジアゾキサイドの副作用として，一過性群49人中20人(40.8%)に30事例（乏尿・浮腫12例，うっ血性心不全5例，多毛3例，黄疸2例，低血圧2例，白血球減少症2例，貧血2例，血小板減少症1例，肝機能障害1例），持続性群57人中26人（45.6%）に35事例（多毛16例，乏尿・浮腫12例，うっ血性心不全3例，白血球減少症1例，好酸球増多1例，血小板減少症1例，嘔吐1例）の報告があった．乏尿・浮腫，うっ血性心不全は106人中25人（23.6%）に認めた．多毛を除く副作用の頻度は一過性群と持続性群で有意差はみられなかった(p>0.05)．またジアゾキサイドを使用した症例のうち，乏尿・浮腫，うっ血性心不全を認めた症例と認めなかった症例で出生体重のパーセンタイル値に有意差を認めなかった(p>0.05)．さらにジアゾキサイド使用量と水分貯留（浮腫・乏尿，うっ血性心不全）の頻度に有意な相関はみられなかった(p>0.05).

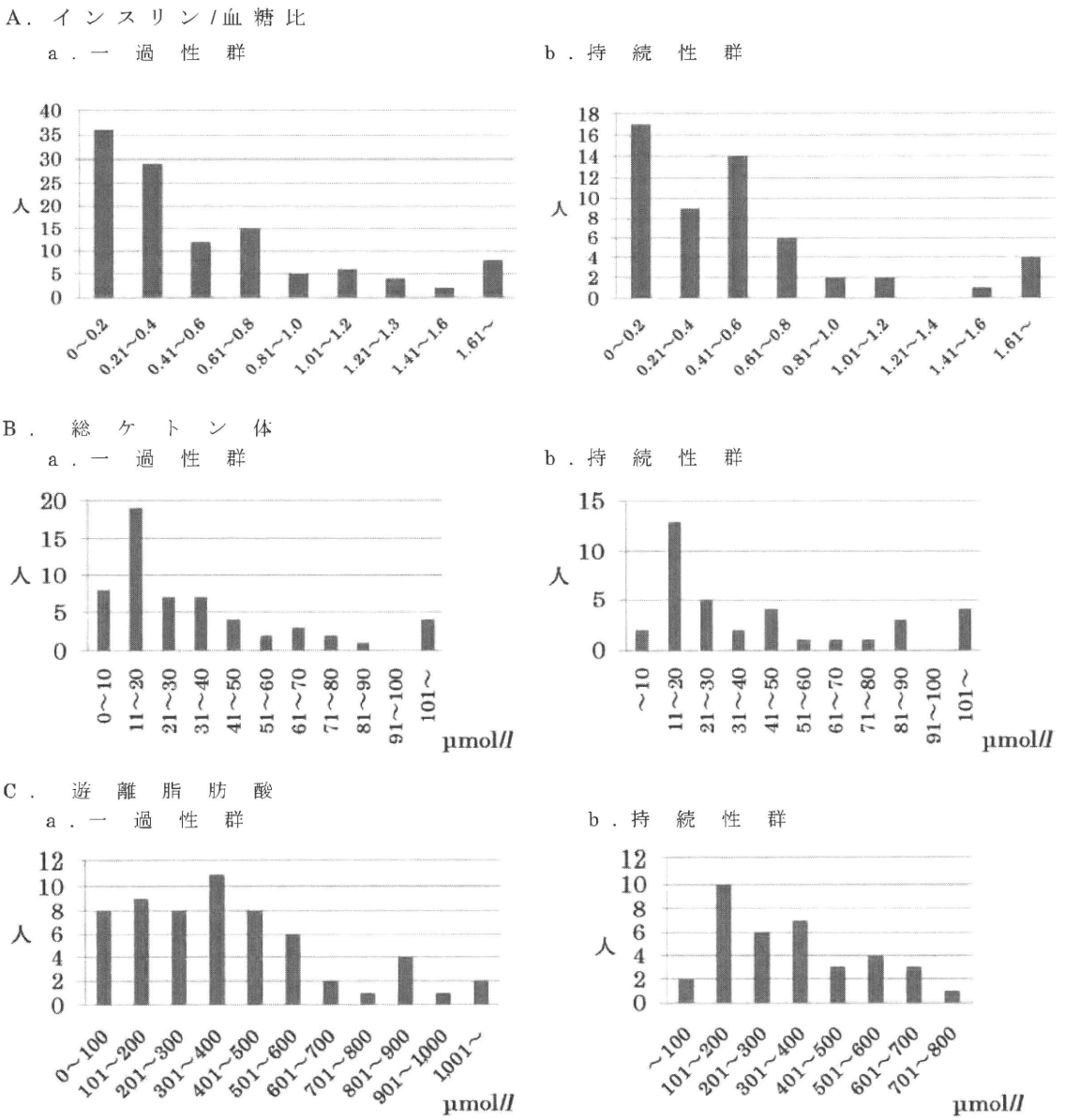


図3　低血糖時の血液検査データ
低血糖時のA.インスリン/血糖比，B.総ケトン体，C.遊離脂肪酸は一過性群，持続性群で有意差は認められなかった（それぞれ $p>0.05$）.

オクトレオチドの副作用として，両群併せて22人中2人に消化器症状（詳細不明）ないし壁在胆石を認めた．またグルカゴン投与により消化器症状(詳細不明)が19人中2人にみられた．

⑨遺伝子診断

持続性群の61人中25人(41.0%)に施行され，そのうち遺伝子検査の結果についても調査出来たのは19人であった．*ABCC8*の両アレル変異1人，片アレル変異5人と，*KCNJ11*の片アレル変異が1人存在し，残りの12人には明らかな変異はみられなかった．

⑩外科治療

持続性群の7人(11.5%)に施行され，うち4人に膵亜全摘術(85～98% 切除)，3人に膵部分切除術が施行された．5人が治癒し，膵亜全摘術(95%)1人と膵部分切除術(膵頭～鉤部核出術)1人の計2人に低血糖が残存した．膵亜全摘術の2人(95%，98% 切除)に糖尿病発症を認めた．病理学的には局所性もしくは多発性の膵島過形成が6人，びまん性の膵島過形成が1人で，遺伝子検査の結果（両アレル変異ではびまん性病変を，父由来の片アレル変異では局所性病変もしくは多発性病変を示唆）と一致していた．

⑪神経学的後遺症

最近2年間に発症した症例の短期予後のみであるが，頭部MRI上変化がみられるもの，発達に遅れがみ

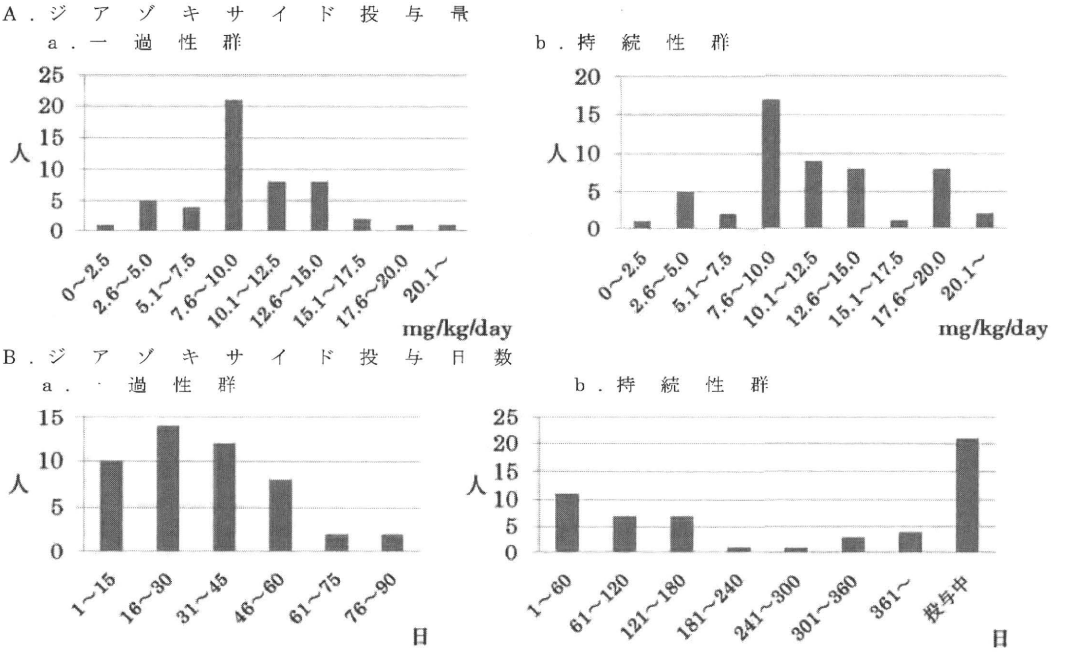


図4 ジアゾキサイド投与量，投与日数
ジアゾキサイド投与量は一過性群，持続性群で有意差は認められなかった（$p>0.05$）．持続性群で長期にジアゾキサイドが投与されているが，副作用の頻度は両群とも同程度であった．

られるものなどで軽微なものも含めると（染色体異常による評価不能例を除く），一過性群15人（11.8%），持続性群10人（16.4%）に神経学的後遺症を認めた．先天性高インスリン血症以外に明らかな原因のあるものを除外すると，両群合わせて15人（8.0%）となり，発達遅滞6人，頭部MRIの拡散強調画像で両側後頭葉を中心に高信号3人，脳室周囲白質軟化症3人，両側中頭蓋窩の脳実質外腔・大槽の拡大1人，West症候群1人，嚥下障害1人であった．

考　察

本調査により，従来明らかでなかった本邦における先天性高インスリン血症の発症頻度，治療実態が解明された．持続性本症の発症頻度は欧米での報告（5万出生に1人）と比較的近かったが，調査票回収率が60%程であるため実際にはさらに症例数が多い可能性が考えられた．しかし他方では，一過性の可能性が高いと思われる低出生体重児やストレス下に出生した児に対してジアゾキサイドが投与され，有効であったために低血糖再発の懸念から生後3か月を超えて投与が続けられている症例が持続性に分類されている可能性もある．一過性本症に関しては，従来の文献通りSGAの男児に多くみられたが，発症率は27,000～50,000人出生に1人の発症率よりも多く，数日以内に改善する軽症例が多く含まれたためと考えられた[3]．

ジアゾキサイドは本邦で本症に対する保険適応のある唯一の薬剤であるが，従来多毛以外の副作用は少ないと考えられてきた．しかしながら，本調査では主に水分貯留によると思われる副作用が稀ではなく，また一過性本症に多い低出生体重児においては水分貯留が容易に心不全や頻脈等の比較的重症の合併症につながる可能性もあり，その使用には慎重になる必要性があると考えられた．

上記の理由で，臨床的には早期に一過性本症と持続性本症を鑑別することが望ましいが，今回の調査では両者を鑑別できるのは在胎週数，出生体重パーセンタイル値のみで，重症度や検査値からの鑑別は難しいことが明らかになった．現時点では，比較的出生体重が大きく，出生時ストレスが少なかったと考えられる児，また遅発発症の児は持続性の可能性が高いとして対処し，低出生体重や他の合併異常を伴う児では一過性の可能性が高いと考えて適切な時点で内科治療の中止を試みることが妥当であると思われるが，より正確な鑑別方法の開発が待たれるところである．

本症の診療に当たって最も注意すべきことは，低血糖による神経学的後遺症を予防することである．今回の調査では観察期間が短いため，長期神経予後は明らかではなかったが，短期的にも様々な神経学的後遺症が観察された．今後コホートとして長期予後の調査が行われることが望ましい．

持続性本症の診療においては，近年膵臓の局所に病変が限局しており，合併症の多い膵亜全摘ではなく局

所切除で後遺症なく治癒する症例が手術例の40% 前後存在することが海外から報告されている[6]. 本邦においても，我々は遺伝子検査で父由来の片アレルの K_{ATP} チャネル変異があった場合，局在病変と考えられるため，18F-DOPA PET，選択的カルシウム動注負荷試験を行って病変部位を同定し，可能なら部分切除を行っているが[9]，現時点では国内ではほとんど局在病変の診断は行われていないのが現況である．また，内科的治療も最近になってようやくジアゾキサイドの保険適応が認められたのみでオクトレオチドやグルカゴンは有用であるにも関わらず適応外治療である．本調査により得られた知見を元にして本邦での診療体制の早期確立が望まれるところである．

本研究は平成21～22年度厚生労働省難治性疾患克服研究事業の一環として行った（H21-難治-一般-189，H22-難治-一般101，研究代表者　依藤　亨）．アンケート調査にご協力頂いた，全国の小児科，新生児科の先生方に深謝致します．

日本小児科学会の定める利益相反に関する開示事項はありません．

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Clinical Characteristics of Congenital Hyperinsulinemic Hypoglycemia in Infant : A Nationwide Epidemiological Survey in Japan

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To clarify the clinical features of congenital hyperinsulinemia in Japan, we conducted a nationwide epidemiological study. Data from 188 patients with hyperinsulinemic hypoglycemia who were born between October 2007 and September 2009 were collected from 624 hospitals with Departments of Pediatrics or Neonatology and more than 300 beds. The collection rate was 59.0%.

One hundred twenty seven patients showed transient hyperinsulinemic hypoglycemia (THI) that was curable within 3 months and 61 patients showed persistent hyperinsulinemic hypoglycemia (PHI). The annual incidence per live births was approximately 1 in 17,000 infants for THI, approximately 1 in 35,400 infants for PHI. Birth weight percentile by gestational age was lower in the THI group than in the PHI group, and it was considered that infants with small for gestational age and transient stress-induced hypoglycemia accounted for a large share of THI group.

There were no differences in blood examination data, such as IRI/BG ratio, total ketone bodies and free fatty acids, between the THI group and the PHI group. Diazoxide was administered to 106 patients and the adverse effects of congestive heart failure, edema and oliguria were found in 25 patients (23.6%). Octreotide was administered to 22 patients, and gallstone and gastrointestinal symptoms were found in 2 patients.

Seven patients (11.5%) in the PHI group underwent partial or subtotal pancreatectomy. Five patients were cured of hypoglycemia, but 2 patients who underwent subtotal or near-total pancreatectomy developed insulin dependence. Two patients who underwent partial pancreatectomy and subtotal pancreatectomy respectively remained hypoglycemic.

After excluding cases showing obvious other causes, neurological complications due to congenital hyperinsulinemia was observed in 15 patients (8.0%) in both groups combined. However, it is difficult to discuss the neurological prognoses of these two groups because of the short observation period to date. In the future, neurological problems should be clarified by a long-term follow up survey. It is hoped that our survey will contribute to elucidating the clinical features of hyperinsulinemic hypoglycemia, so that therapeutic strategies for congenital hyperinsulinism in Japan can be established.

Brief Report—Endocrine Research

Molecular and Clinical Analysis of Japanese Patients with Persistent Congenital Hyperinsulinism: Predominance of Paternally Inherited Monoallelic Mutations in the K_{ATP} Channel Genes

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Background: Preoperative identification of the focal form of congenital hyperinsulinism is important for avoiding unnecessary subtotal pancreatectomy. However, neither the incidence nor the histological spectrum of the disease is known for Japanese patients.

Aims: The aim of the study was to elucidate the molecular and histological spectrum of congenital hyperinsulinism in Japan.

Subjects: Thirty-six Japanese infants with persistent congenital hyperinsulinism were included in the study.

Methods: All exons of the ATP-sensitive potassium channel (K_{ATP} channel) genes (*KCNJ11* and *ABCC8*), the *GCK* gene, and exons 6 and 7 and 10–12 of the *GLUD1* gene were amplified from genomic DNA and directly sequenced. In patients with K_{ATP} channel mutations, the parental origin of each mutation was determined, and the results were compared with the histological findings of surgically treated patients. In one of the patients with scattered lesions, islets were sampled by laser capture microdissection for mutational analysis.

Results: Mutations were identified in 24 patients (66.7%): five in *GLUD1* and 19 in the K_{ATP} channel genes. Sixteen had a paternally derived, monoallelic K_{ATP} channel mutation predictive of the focal form. In 10 patients who underwent pancreatectomy, the molecular diagnosis correctly predicted the histology, more accurately than [18F]-3,4-dihydroxyphenylalanine positron emission tomography scans. Three patients showed focal lesions that occupied larger areas of the pancreas. Preferential loss of the maternal allele was observed in these islets.

Conclusion: The majority of the Japanese patients with K_{ATP} channel hyperinsulinism (84.2%) demonstrated paternally inherited monoallelic mutations that accurately predicted the presence of the focal form. ***(J Clin Endocrinol Metab* 96: E141–E145, 2011)**

Persistent congenital hyperinsulinism is the main cause of prolonged hypoglycemia in infancy. The most common etiology is an inactivating mutation in one of two genes, *ABCC8* or *KCNJ11*, which code for the two subunits of the pancreatic ATP-sensitive potassium (K_{ATP}) channel. The second most common is an activating mu-

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Abbreviations: DOPA, 3,4-Dihydroxyphenylalanine; GCK, glucokinase; GLUD1, glutamate dehydrogenase; K_{ATP}, ATP-sensitive potassium channel; MLPA, multiple ligation-dependent probe amplification; PET, positron emission tomography.

tation in the glutamate dehydrogenase (*GLUD1*) gene, which is found in cases of hyperinsulinemia-hyperammonemia syndrome followed by an activating mutation in the glucokinase (*GCK*) gene with a much rare incidence (1).

Because severely affected infants often experience profound neurological sequelae (2, 3), appropriate management of hypoglycemia is critically important. Infants resistant to medical treatment usually undergo subtotal pancreatectomy. Although the procedure is often effective at controlling hypoglycemia, residual hypoglycemia is not uncommon, and many of the infants develop insulin-dependent diabetes mellitus postoperatively (1, 4).

Notably, the recognition of the focal form of persistent congenital hyperinsulinism has changed clinical practice because precise pre- and intraoperative identification of focal lesions allows us to perform a partial resection of the pancreas, leading to a complication-free cure (1, 5, 6).

Focal lesions are found in individuals with a paternally inherited, monoallelic K_{ATP} channel mutation (5–7). Subsequent somatic loss of the maternal allele (most likely caused by paternal isodisomy) leads to a loss of the activities of the K_{ATP} channel and the adjacent tumor suppressors (*H19* and *CDKN1C*) normally expressed by the maternal allele. These cells gain a growth advantage eventually forming a focal lesion of insulin-overproducing β-cells (8).

It has been reported that approximately 40% of patients with K_{ATP} channel hyperinsulinism have monoallelic mutations (9, 10) and that up to 40–60% of surgically treated patients have the focal form (1, 6, 7). However, to date, neither the incidence of focal lesions nor the clinical spectrum of persistent congenital hyperinsulinism has been reported for Asians.

In this study, we performed a comprehensive mutational analysis of Japanese patients with this disorder and correlated the results with the histology of surgically treated patients.

Subjects and Methods

Subjects

The study subjects were 36 Japanese infants with persistent congenital hyperinsulinism. The inclusion criteria were as follows: 1) a plasma insulin level of greater than 3 μU/ml in the presence of hypoglycemia [plasma glucose < 45 mg/dl (2.5 mmol/liter)], 2) hypoglycemia lasting beyond 3 months of age, and 3) the absence of insulinoma. The patients were born in 2005–2010 except for those with hyperinsulinemia-hyperammonemia syndrome who were recruited over a longer period (born in 1999–2009). For mutational analysis, written informed consent was obtained, and the study protocol was approved by the institutional review board.

Mutational analysis

Genomic DNA was extracted from peripheral blood leukocytes using a QIAmp DNA blood kit (QIAGEN, Hilden, Germany) as recommended by the supplier. Then all exons and the exon-intron boundaries of the *KCNJ11*, *ABCC8*, and *GCK* genes were amplified from genomic DNA. For the *GLUD1* gene, only exons 6 and 7 (the antenna domain) and exons 10–12 (the GTP binding domain) were amplified because previously reported mutations were exclusively found in these regions. The amplification conditions and the sequences of the primers are available as supplemental data, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. The amplified products were purified using the Wizard PCR Preps DNA purification system (Promega, Fitchburg, WI) and directly sequenced using the BigDye Terminator cycle sequencing kit (version 3.1; Applied Biosystems, Foster City, CA).

Deletion mutations that might not have been detected by the PCR-sequencing strategy described above were analyzed by multiple ligation-dependent probe amplification (MLPA) of all 39 exons of the *ABCC8* gene. The analyses were performed using SALSA MLPA kit P117 (MRC Holland, Amsterdam, The Netherlands) as recommended by the manufacturer.

[18F]-3,4-dihydroxyphenylalanine (DOPA) positron emission tomography (PET)

[18F]-DOPA PET studies were performed at the PET facility of Kizawa Memorial Hospital basically, as described by Ribeiro *et al.* (11). The scan results were fused with those of a computed tomography scan taken at the same time to localize the focal lesion more accurately.

Laser capture microdissection (LCM)

The scattered islets of patient 10 were sampled by LCM using the PixCell IIe LCM system (Arcturus, Mountain View, CA). DNA was extracted from the pooled islets using a FASTPURE DNA kit (Takara-bio, Ohtsu, Japan). DNA extracted from a normal pancreatic area on the same slide was used as the control.

Results

Patient profiles and mutations

The profiles of the patients and the results of the mutational analyses are listed in Table 1. In patients with elevated ammonia at the initial presentation, only patients 1–5 showed persistent hyperammonemia. Those five had mutations in *GLUD1*. Of the remaining 31 patients, mutations were identified in 19 (61.3%): 18 in *ABCC8*, one in *KCNJ11*, and none in *GCK*. No exonic deletions were identified by MLPA, and the four novel missense mutations were not found in 100 normal controls. p.R836X and p.R998X in *ABCC8* were identified in five and three unrelated patients, respectively, possibly representing relatively common mutations in Japanese.

Interestingly, of these patients with K_{ATP} channel mutations, only two had biallelic mutations, whereas the

TABLE 1. Profiles of the patients with mutations

Patient no.	Gender	Onset	Glucose (mg/dl) [mmol/liter]	Insulin (μU/ml) [pmol/liter]	Ammonia (μg/dl) [μmol/liter]	Mutation					Medical treatment
						Gene	cDNA	Protein	Previously reported?	Parental origin	
1	F	9 months	38 [2.1]	4.8 [33]	83 [49]	*GLUD1*	c.661C>T	p.R221C	yes	ND	F, D
2	M	7 months	30 [1.7]	3 [21]	132 [77]	*GLUD1*	c.797A>G	p.Y266C	yes	ND	F, D
3	F	3 months	29 [1.6]	4 [28]	246 [144]	*GLUD1*	c.1336G>A	p.G446S	Yes	ND	F, D
4	M	10 months	<45 [2.5]	7.7 [53]	154 [90]	*GLUD1*	c.1229A>G	p.N410S	No	ND	F, D
5	M	0 d	10 [0.6]	10 [69]	250 [147]	*GLUD1*	c.1229A>C	p.N410T	Yes	ND	F, D
6[a]	F	2 d	31 [1.7]	30.2 [210]	78 [46]	*ABCC8*	c.382G>A c.3748C>T	p.E128K p.R1250X	Yes, Yes	Biparental	
7	M	2 d	5 [0.3]	7.5 [52]	131 [77]	*ABCC8*	c.2506C>T c.4575_4587del13	p.R836X p.M1524Mfs1539X	Yes, No	Biparental	F, O
8	M	0 d	<45 [2.5]	11 [76]	58 [34]	*ABCC8*	c.4516G>A	p.E1506K	Yes	Mat	F, D
9[a]	F	1 month	<20 [1.1]	42.4 [294]	NA	*ABCC8*	c.2506C>T	p.R836X	Yes	Pat	
10[a]	M	2 d	10 [0.56]	23.5 [163]	NA	*ABCC8*	c.4412-13G>A	—	Yes	Pat	
11[a]	F	0 d	33 [1.8]	46.6 [324]	79 [46]	*ABCC8*	c.3745G>T	p.V1249F	No	Pat	
12[a]	F	3 months	20 [1.1]	5.16 [36]	78 [46]	*ABCC8*	c.2992C>T	p.R998X	Yes	Pat	
13[a]	F	0 d	23 [1.3]	101 [701]	45 [24]	*ABCC8*	c.4608 + 1G>A	—	No	Pat	
14[a]	M	0 d	22 [1.2]	22.7 [158]	75 [44]	*ABCC8*	c.2992C>T	p.R998X	Yes	Pat	
15[a]	M	5 months	33 [1.8]	5.42 [38]	NA	*ABCC8*	c.2992C>T	p.R998X	Yes	Pat	
16[a]	M	0 d	28 [1.6]	38.7 [269]	66 [39]	*ABCC8*	c.331G>A	p.G111R	Yes	Pat	
17	F	2 months	15 [0.8]	9.9 [69]	90 [53]	*ABCC8*	c.61_62insG	p.V21Gfs88X	No	Pat	F, O
18	M	0 d	19.6 [1.1]	44 [306]	79 [46]	*ABCC8*	c.2506C>T	p.R836X	Yes	Pat	F, O
19	F	7 months	35 [1.9]	11.2 [78]	97 [57]	*ABCC8*	c.2506C>T	p.R836X	Yes	Pat	F, O
20	M	4 months	<45 [2.5]	7.5 [52]	84 [49]	*ABCC8*	c.3928_3929insG	p.A1310Gfs1405X	No	Pat	F, O
21	M	2 d	38 [2.1]	3.4 [24]	91 [53]	*ABCC8*	c.4186G>T	p.D1396Y	No	Pat	F
22	F	0 d	9 [0.5]	22 [153]	NA	*ABCC8*	c.2506C>T	p.R836X	Yes	Pat	F, O
23	M	2 d	0 [0]	17.3 [120]	317 [186]	*ABCC8*	c.4412-13G>A	—	Yes	Pat	F, D
24[a]	M	0 d	33 [1.8]	21.9 [152]	75 [44]	*KCNJ11*	c.637G>A	p.A213T	No	Pat	

The clinical data are those at the initial presentation. Of the medically treated patients with monoallelic, paternally inherited K_{ATP} channel mutations (patients 17–23), none reported a family history of hypoglycemia. F, Frequent feeding; D, diazoxide; O, continuous sc injection of octreotide; M, male; F, female; Pat, paternal; Mat, maternal; NA, not available; ND, not determined.

[a] Patients who underwent surgery.

other 17 had monoallelic mutations. Furthermore, 16 of 17 of the mutations were of paternal origin. The single maternally inherited mutation was identical to a mutation previously reported by Huopio *et al.* (12) as a mutation causing hyperinsulinism in infancy and diabetes mellitus in adulthood. In fact, the mother of the patient developed diabetes at the age of 13 yr, and the maternal grandmother developed a mild form of diabetes during adulthood. Therefore, from the results of the mutational analyses, the incidence of a paternally inherited monoallelic mutation suggesting the presence of a focal lesion appears to be much higher in Japanese (84.2% of K_{ATP} channel hyperinsulinism cases).

Clinical studies and LCM studies

None of the patients with paternally inherited K_{ATP} channel mutations responded to diazoxide except for patient 23 who partially responded at the maximal dose of 25 mg/kg · d. Pancreatectomy was performed on 10 patients who were resistant to medical therapy, one with a biallelic *ABCC8* mutation (patient 6) and nine with monoallelic paternally inherited mutations, eight in *ABCC8* (patients 9–16), and one in *KCNJ11* (patient 24). [18F]-DOPA PET scans were performed in all patients preoperatively. The patient with the biallelic mutation (patient 6) showed typical diffuse uptake. Of the nine patients with monoallelic mutations, four showed a single focal uptake pattern (patients 9, 12, 15, and 16); two (patients 14 and 24) showed multifocal uptake; and the other three (patients 10, 11, and 13) showed irregular uptake throughout the pancreas, which was difficult to distinguish from that o diffuse lesions. The six patients with focal or multifocal uptake underwent partial resection of the pancreas. Histological examination revealed a single focal lesion in these patients. Five were almost completely cured, and one showed residual but milder hypoglycemia. Of the three patients who demonstrated irregular uptake during the PET study, two underwent subtotal pancreatectomy because their intraoperative findings did not rule out the presence of diffuse lesions. In one of these two patients (patient 13), postoperative histology revealed a large focal lesion in the tail and the body of the pancreas. In the other patient (patient 11), abnormal islets were found throughout the pancreas. The presence of normal islets in part of the pancreas suggested the diagnosis of a giant focal lesion. In the third patient (patient 10) with irregular [18F]-DOPA uptake (Fig. 1B), an arterial stimulation venous sampling study suggested the presence of a lesion in the body or the tail of the pancreas (Fig. 1A). Intraoperatively, no focal lesion could be identified by inspection or palpation. Although the margins of the lesion could not be clearly determined, partial resection was performed at 2.5 cm from the tail. This patient was also clinically cured after surgery. Postoperative histology revealed scattered, relatively large islets with a diameter of up to 700 μm clustered within the tail and the body. Each islet appeared to be separated by normal acinar cells, and no

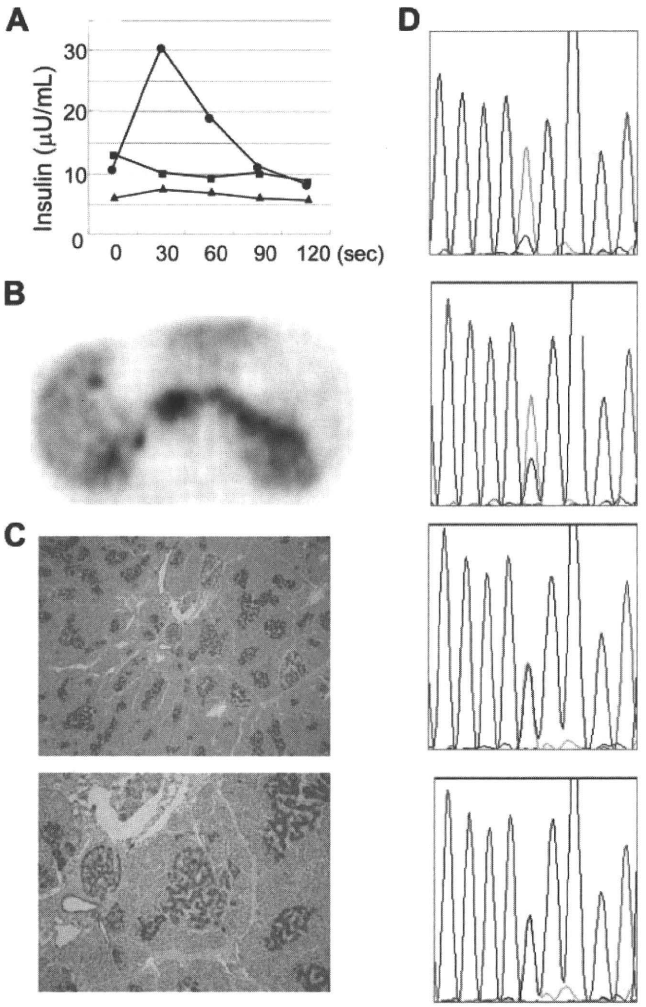

FIG. 1. Results of different diagnostic modalities in patient 10. A, Results of arterial stimulation venous sampling studies. The insulin concentration of the right hepatic vein was measured after the injection of calcium into the splenic (*filled circles*), gastroduodenal (*filled rectangles*), and superior mesenteric (*filled triangles*) arteries. An insulin response was observed only after stimulation of the splenic artery. B, A curved planar reconstruction of a [18F]-DOPA PET scan. The uptake in the head probably reflects an artifact. C, Chromogranin A staining of the resected pancreas showing the area in which abnormal islets were most densely distributed. Magnification, ×40 (*upper panel*), ×80 (*lower panel*). D, Mutational analysis of abnormal islet samples. The *upper two panels* show the results of two separate analyses of 30 (*upper panel*) and 40 (*lower panel*) islet samples. The *lower two panels* show the results of a similar analysis of an adjacent normal pancreatic area. The paternally inherited A allele (*green*) predominates in the abnormal islets, whereas the A and the wild-type G alleles (*black*) have similar intensities in the normal area of the pancreas.

single lesion composed of a solid β-cell cluster was identified by serial sections of the specimen (Fig. 1C). LCM was performed twice to collect samples from 30 and 40 of these islet clusters. Mutational analysis of the pooled DNA collected from these LCM samples revealed the predominance of the paternally inherited mutant allele within these scattered large islets compared with the surrounding normal pancreatic tissue (Fig. 1D).

Discussion

The most important finding of this study is the higher incidence of paternally inherited, monoallelic K_{ATP} channel mutations in Japanese patients with congenital hyperinsulinism ($P < 0.005$ by the sign test), which suggests that the majority of Japanese patients have the focal form. Although the number of patients is small, we believe our results represent the situation of the whole country for several reasons. First, a national survey in 2008–2009 conducted by the Ministry of Health, Labor, and Welfare of Japan estimated the incidence of persistent congenital hyperinsulinism as 1:35,400 births. Our study captured 23% of all cases during that period. Second, the patients were referred without geographical biases because ours is the only laboratory currently offering a comprehensive molecular diagnosis in Japan. Third, a previous report by Ohkubo *et al.* (13) also reported a high frequency (seven of 10) of monoallelic mutations in Japan. In contrast, patients with hyperinsulinism-hyperammonemia syndrome were collected somewhat arbitrarily over a longer period; therefore, the apparent higher incidence might not represent the actual incidence in Japan.

Conflicting results have been reported for the diabetogenesity of p.E1506K in *ABCC8* (12, 14, 15). The association might be a chance observation or might reflect a difference in the genetic background. If the association does exist, that might be due to the specific nature of the mutation, which confers the instability of the β-cells such as altered membrane potential of the cells.

Molecular diagnosis correctly predicted the histology in all patients who underwent pancreatectomy. On the contrary, the ability of [18F]-DOPA PET scans to identify focal lesions was inferior compared with the results of previous reports for other populations (16, 17). Histologically, at least two patients with ambiguous PET results had large focal lesions. The third patient (patient 10) appeared to have unusually scattered islets for a focal lesion. However, there remains the possibility that these islets are actually interconnected and represents a focal lesion with greater admixture of exocrine tissues. Although the number of patients was too small to draw a definite conclusion, larger lesions might be more common in the Japanese.

The reason that the incidence of the focal form of the disease is higher in Japanese is unclear. One possibility is that Japanese have a higher incidence of somatic isodisomy. If this occurred during the earlier stages of development, it would lead to the development of Beckwith-Wiedemann syndrome. However, the incidence of this syndrome caused by paternal isodisomy is not particularly higher in Japanese (18). Alternatively, cells with mutations common in Japanese might be more prone to develop into

a focal lesion, by either promoting a second hit of isodisomy or conferring a growth advantage after the disomic event. Further studies are necessary to address this question.

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ORIGINAL ARTICLE

Diagnostic accuracy of [^{18}F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan

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Summary

Objective We aimed to elucidate the accuracy and limitations of [^{18}F]-fluoro-L-dihydroxyphenylalanine ([^{18}F]DOPA) positron emission tomography (PET) for Japanese patients with congenital hyperinsulinism. Although [^{18}F]DOPA PET is reported to be useful for precisely localizing the focal form of congenital hyperinsulinism, previous reports are mostly from European and North American centres.

Patients Seventeen Japanese infants with congenital hyperinsulinism.

Measurements [^{18}F]DOPA PET studies were carried out, and the results were assessed by simple inspection or by a quantitative measurement termed the 'Pancreas Percentage', which expresses the uptake of the head, body or tail of the pancreas as a percentage of the total maximum standardized uptake value of the whole pancreas. The results were compared with those of other studies, including genetic analysis and histology.

Results By simple inspection, when a single focal uptake was obtained, the localization and histology were correct in all cases that underwent pancreatectomy. However, the overall results were consistent with the molecular diagnosis and histology in only 7/17 and 6/12 patients, respectively. The inaccuracy of PET studies by inspection was because of elevated background uptake that mimicked a diffuse or multifocal appearance. The accuracy improved substantially using the Pancreas Percentage; it was consistent with the molecular diagnosis and histology in 10/17 and 9/12 patients, respectively.

Conclusions In contrast to the results of previous reports, [^{18}F]DOPA PET appears to be less efficient for diagnosing Japanese patients with congenital hyperinsulinism. However, the diagnostic accuracy is substantially improved when this technique is combined with the Pancreas Percentage.

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Introduction

Congenital hyperinsulinism in infancy is characterized by prolonged hyperinsulinism and severe hypoglycaemia. This disorder is most often associated with inactivating mutations in one of two genes, *ABCC8* and *KCNJ11*, which encode the two subunits of the pancreatic ATP-sensitive potassium (K_{ATP}) channel.[1,2]

There are two main histopathological forms of K_{ATP} channel hyperinsulinism: diffuse and focal.[1,3] In the diffuse form, mutations are present in both alleles of the K_{ATP} channel genes; this form is associated with insulin oversecretion from all β cells in the pancreas. In the focal form, a mutation is present in the paternal allele.[4,5] The subsequent somatic loss of the maternal allele containing the K_{ATP} channel genes and the adjacent paternally imprinted tumour-suppressor genes lead to a growth advantage for insulin-overproducing β cells, which eventually form a focal lesion in the pancreas.

As uncontrolled severe hypoglycaemia causes neurological complications, surgical treatment is required if medical treatment is not effective. The diffuse form is usually treated by subtotal pancreatectomy. Although this surgery is effective for controlling hypoglycaemia, many patients develop insulin-dependent diabetes mellitus postoperatively. In contrast, the focal form can be cured by a partial pancreatectomy without complications as long as the localization of the lesion is known pre- or intra-operatively.

In 2003, Otonkoski *et al.*[6] reported that positron emission tomography (PET) using [^{18}F]-fluoro-L-dihydroxyphenylalanine ([^{18}F]DOPA) effectively localizes focal lesions. Since then, several studies have reported the efficacy of [^{18}F]DOPA PET scanning for

detecting the localization of focal lesions.[2,7–11] However, previous studies mainly focus on Caucasian subjects, there are no comprehensive [^{18}F]DOPA PET studies on Asian subjects.

In a previous study on the molecular analysis of Japanese patients,[7] we briefly reported the PET appearance of 10 surgically treated patients. In the present study, we extended the analysis to include more patients who were treated with or without surgery. We unexpectedly encountered difficulties in diagnosing Asian subjects, which was in contrast with previous studies with subjects of other ethnicities. In an attempt to overcome the ambiguity of the interpretation of PET results, we employed a quantitative method for the evaluation of pancreatic [^{18}F]DOPA uptake.

Subjects and methods

Subjects

The study population included 17 Japanese infants (nine boys and eight girls; age 2 years and 37 months) with persistent congenital hyperinsulinism who were referred to Kizawa Memorial Hospital, Japan, between July 2005 and June 2010. Diagnoses were based on the following criteria: (i) plasma insulin level >3 μU/ml in the presence of hypoglycaemia [plasma glucose <45 mg/dl (2·5 mM)], (ii) hypoglycaemia lasting beyond 3 months of age and (iii) the absence of an insulinoma. The demographic features of the patients are shown in Table 1. Written informed consent was obtained from their guardians, and the study protocol was approved by the Institutional Review Board. In this study, we also included patients with biallelic mutations in the K_{ATP} channel genes, in whom diffuse lesions were expected. The guardians were told that the PET study would only serve to confirm the diffuse nature of the disease and that part of the study's purpose was for this population to serve as a control for future patients.

[^{18}F]DOPA PET analysis

[^{18}F]DOPA PET studies were performed using an ADVANCE NXi scanner (GE, USA) at Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, as described by Ribeiro *et al.*[8]

If the patient was on diazoxide or glucagon, these were discontinued for at least 2 days before the study, whereas octreotide treatment was continued. Prior to the study, patients fasted for 6 h and normoglycaemia was maintained by intravenous glucose infusion. PET acquisition was performed under light sedation with thiamylal sodium.

[^{18}F]DOPA was manufactured on the day of the study using CYPRIS-HM18 cyclotron (Sumitomo, Japan). After 3 min of transmission scanning, [^{18}F]DOPA (5 MBq/kg) was infused intravenously over 1 min. Five-minute acquisitions of PET scanning (in the two-dimensional acquisition mode) were consecutively performed for up to 60 min. The PET scan results were incorporated with those of a CT scan taken simultaneously to localize the focal lesion more accurately.

Table 1. [^{18}F]DOPA PET analysis of 17 patients with congenital hyperinsulinism, and comparison with genetic, ASVS and histology results

Patient/sex	Origin/gene	Diagnosis by histology	Age at PET (months)	Diagnosis by inspection	Standardized uptake value			Pancreas %			Diagnosis by pancreas %	Diagnosis by ASVS
					Head	Body	Tail	Head	Body	Tail		
Surgery												
1/F	Bip/ABCC8	Diffuse	4	Diffuse	6·3	5·8	4·6	100	92	73	Diffuse	No
2/M	Bip/ABCC8	Diffuse	2	Diffuse	5·1	3·8	4·0	100	75	78	Diffuse	No
3/F	Bip/ABCC8	Diffuse	37	Diffuse	9·0	7·7	6·7	100	86	74	Diffuse	Focal (H)
4/F	Pat/ABCC8	Focal (H)	13	Focal (H)	6·9	3·6	2·8	100	52	41	Focal (H)	Focal (H)
5/F	Pat/ABCC8	Focal (H)	7	Focal (H)	5·7	3·8	3·0	100	67	53	Focal (H)	No
6/M	Pat/ABCC8	Focal (H)	2	Focal (H)	4·5	2·9	2·8	100	64	62	Focal (H)	No
7/M	Pat/KCNJ11	Focal (H)	2	Irregular (H, B)	3·8	2·5	2·5	100	66	66	Focal (H)	No
8/M	Pat/ABCC8	Focal (B)	2	Irregular (H, B)	4·4	7·1	2·4	62	100	34	Focal (B)	Focal (B)
9/M	Pat/ABCC8	Focal (H)	8	Not detected	1·8	2·1	1·6	86	100	73	Not detected	Focal (H)
10/F	Pat/ABCC8	Large focal (B, T)	5	Irregular (H, B)	2·4	3·7	1·8	65	100	49	Focal (B)	No
11/M	Pat/ABCC8	Large focal (B, T)	17	Irregular	6·8	5·3	5·0	100	78	74	Diffuse	Focal (B, T)
12/F	Pat/ABCC8	Large focal (H, B, T)	4	Irregular	4·0	4·1	4·1	98	100	100	Diffuse	No
No surgery												
13/M	Pat/ABCC8	(complete remission)	9	Focal (T)	2·4	2·9	5·0	48	58	100	Focal (T)	Normal
14/M	Pat/ABCC8	(partial remission)	5	Irregular	5·1	4·7	7·0	73	67	100	Diffuse (H, T)	No
15/M	Pat/ABCC8	(partial remission)	23	Irregular	4·5	3·7	3·4	100	82	76	Diffuse	No
16/F	Pat/ABCC8		16	Irregular	3·8	3·8	2·9	100	100	76	Diffuse	Diffuse
17/F	Pat/ABCC8		26	Diffuse	6·0	5·4	6·3	95	86	100	Diffuse	No

M, male; F, female; Bip, biparental mutation; Pat, paternal mutation; Diffuse, diffuse lesion/uptake; Focal, focal lesion/uptake; Irregular, irregular uptake; H, head of the pancreas; B, body of the pancreas; T, tail of the pancreas; complete remission, without any treatment; partial remission, frequent feeding alone; ASVS, arterial stimulation venous sampling analysis; [^{18}F]DOPA PET, [^{18}F]-fluoro-L-dihydroxyphenylalanine positron emission tomography.