つ2000年以降の症例においてより良好であった（3年生存率；84% ：55%）。このことは、近年における手術手技、透析管理技術等の進歩だけではなく、PH 1に対する早期診断および治療、脳死下臓器分配システムの改善などが臓器移植後成績向上に貢献しているであろう。欧州からの小児PH 1症例に対する臓器移植成績では、症例数が少ないながら、症例ごとに、pre-emptive に肝単独移植、肝腎異時移植、肝腎同時移植を選択し、生存率だけではなく、術後の長期的な成長発達においても良好な結果であったと報告している。

本邦におけるPH 1に対する臓器移植成績に関しては、日本肝移植研究会におけるレジストリー報告において、2010年度末までに計14例（18歳未満：9例、18歳以上5例）に対して生体肝移植術が施行され、移植後予後は1年・3年・5年患者生存率としてともに50%と、他の代謝性疾患と比較し悪かった。18歳未満小児症例においては、9例中4例が死亡している。本邦においても過去に腎単独移植を選択された症例が存在するが、現時点では、上記のごとく限られた症例においてのみ施行しうる治療と考えられる。

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6. 糖原病

1)　疾患別各論

糖原病はグリコーゲン代謝に関与する酵素の先天的な欠損により、主に肝臓あるいは筋肉にグリコーゲンが蓄積する疾患であり、蓄積する部位により大きく肝筋型、肝型、筋型に分けられる[1]。肝型糖原病はⅠ型、Ⅲ型、Ⅳ型、ⅥおよびⅨ型であり、空腹時低血糖と肝腫大を特徴とする。

・ 糖原病Ⅰ型

糖原病Ⅰ型はglucose-6-phosphatase欠損であるⅠa型とG6P translocase欠損であるⅠb型に分かれる。これらの酵素はグルコース-6-リン酸をグルコースに変換する糖新生にとって重要である。Ⅰ型の臨床症状としては低血糖、高乳酸血症、高脂血症、低身長、人形様顔貌が特徴的である。Ⅰa 型とⅠb 型は糖代謝障害による症状はほとんど同一であるが、Ⅰb型の多くは好中球減少症や好中球機能異常を伴っており、細菌性肺炎、中耳炎、皮膚膿瘍、尿路感染症などの細菌感染を繰り返す。治療方針としては低血糖予防、特に夜間の低血糖予防が重要となる。このため、日中は頻回の食事摂取を行い、夜間は胃内持続注入や未調理のコーンスターチなどが併用される。また、乳糖、蔗糖、ガラクトース、果糖は高乳酸血症を亢進するため摂取制限を行う。Ⅰb型の治療は低血糖予防に加え易感染性の治療が重要な問題となる。granulocyte colony-stimulating factor (G-CSF)や granulocyte macrophage colony-stimulating factor (GM-CSF)の有効性が報告されており[2),3)]、これらの投与により好中球数、機能は正常化し、臨床的には易感染性がなくなるとされている。

・ 糖原病Ⅲ型

グリコーゲンの脱分枝酵素の欠損によりグリコーゲンが蓄積する。肝、筋に酵素欠損が認められるⅢa型と、肝のみに酵素欠損が認められるⅢb型があり、糖新生は正常であるため低血糖の症状は軽度である[4)]。稀に肝硬変や心筋障害を伴うことが報告されている。

・ 糖原病Ⅳ型

グリコーゲン分枝酵素の欠損によりグリコーゲンポリマー（アミロペクチン様物質）が蓄積する。現在では 5 病型が報告されており、肝型（重症肝硬変型）、非進行性肝型、致死新生児神経・筋型、乳児筋・肝型、成人ポリグルコサン小体病がある。機能障害の最も著しいのは肝で、発育不全、筋緊張低下、肝腫大がみられ、典型例では乳児期早期に重度の肝硬変をきたす。

表　肝型糖原病の病型

病型	亜型	欠損酵素	糖原蓄積部位	本邦での移植件数
Ⅰ型	Ⅰa	glucoce-6-phosphatase	肝，腎，小腸上皮	2例
	Ⅰb	transport of G6P		9例
Ⅲ型	Ⅲa	liver & muscle glycogen debranching enzyme	肝，筋	-
	Ⅲb	liver glycogen debranching enzyme	肝	-
Ⅳ型		branching enzyme	肝，筋	4例
ⅥおよびⅨ型	Ⅵ	liver phosphorylase	肝	-
	Ⅸa	liver phosphorylase kinase (X-linked form)	肝	-
	Ⅸb	liver & muscle phosphorylase kinase (autosomal form)	肝，筋	-
	Ⅸc	liver phosphorylase kinase (autosomal form)	肝	-

2）移植適応

移植適応に関しては以下の適応が考えられる。

A，欠損酵素を補充する目的で行う場合

B，肝不全、肝腫瘍の治療目的に行われる場合・肝型糖原病（Ia 型，Ib 型，Ⅲ型、Ⅳ型、ⅥおよびⅨ型）

糖原病に対する内科的治療は効果的であるため、Ia 型についてＡを理由として肝移植を行うケースは稀であり、通常は肝移植を行わず特殊ミルクや内科療法による治療を継続することになるが、移植を行えばこれらの治療はほぼ不要となる。Ib 型で重度の低血糖を回避するため頻回のミルク摂取（注入など）と好中球減少などに対する感染予防が必要である。肝移植を行った場合には低血糖とそれによる中枢神経障害が回避でき、また、合併する好中球減少・機能低下も改善し、感染症や炎症性腸疾患の罹患のリスクも低下する可能性がある。しかし、好中球機能が改善せず、炎症性超疾患の再発を来した症例の報告もみられる。

肝の adenoma はⅠ型で高頻度に出現し、腫瘍からの出血や悪性化が大きな問題となる。Ⅰ型での肝移植を施行された大部分は多発性の adenoma である。切除できない多発性の肝 adenoma や臨床的、病理学的に悪性を示唆する症例など移植適応に関しては良性・悪性、大きさや数に依存する。

稀な IV 型は肝不全を起こす疾患のため肝移植以外での救命は困難である。

3) 予後因子

予後を左右する因子として、低血糖や代謝性アシドーシスなどによる急性代謝性発作（metabolic derangement：MD）がある。欧州からの糖原病Ⅰ型の予後に関する大規模な cohort

study では MD は 71%に認め、死亡症例 16 例のうち 9 例が MD で死亡しており、年齢は 1 歳以下から 8 歳までであり、また、月例が進むにつれ MD の頻度は減少する傾向にあった[5]。肝移植の導入により、糖代謝と合併症が是正されるが、長期的には他の肝移植患者と同様の問題が生じている。また、Ⅰb 患者では好中球機能の予後については不明な点が多く[6],[7]、肝移植後も G-CSF の投与が必要な症例も報告されている[8]。

4) 治療成績

本邦では 15 例の糖原病患児に対して肝移植が行われており、全例が生体肝移植である。Ⅰ型が 11 例（Ⅰa 型 2 例、Ⅰb 型 9 例）、Ⅳ型が 4 例であり、他の肝型糖原病症例は肝移植が行われていない。ドナーは父親 6 例、母親 8 例、祖父 1 例であり、提供時の年齢は 24 歳～61 歳、血液型は identical 11 例、compatible 1 例、incompatible 3 例であった。グラフトのタイプは外側区域 11 例、左葉 4 例（APOLT 1 例を含む）であった。Ⅰa 型の 2 例中 1 例が急性拒絶反応により死亡している。Ⅰb 型は 9 例中 2 例が死亡しており、1 例は出血、感染のより、1 例は肝不全により死亡している。Ⅰb 型の 5 年生存率は 77.8%であった（下図）。また、Ⅰb 型の好中球機能に関しては、肝移植後も G-CSF の投与を必要としている症例もあった。Ⅳ型は 4 例中 3 例死亡しており、1 例は ABO 不適合症例で、急性拒絶反応後の肝不全により再移植後に死亡している。1 例は脾臓摘出術後の門脈血栓に起因していた。

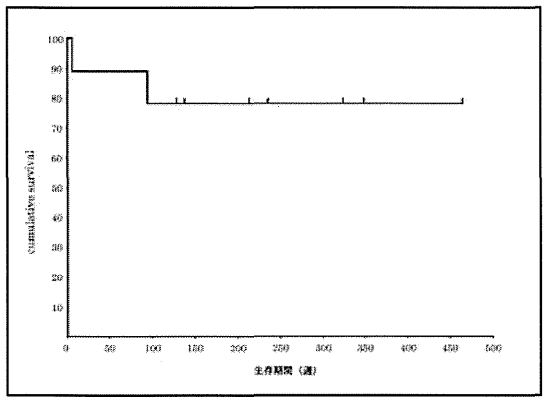

図　糖原病Ⅰb 型の生存率

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Ⅳ. 研究成果の刊行に関する一覧表

○研究成果の発表

平成24～25年度に発表された研究成果は以下のとおりである。

◎は本研究班の課題内容、○は密接に関係する内容である。

[学術雑誌等での公表]

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