Image interpretation

PET images were interpreted by one of the authors, H.N., who is a board-certified radiologist and has experience of over 6870 PET studies. By inspection, focal lesions were identified when the local uptake of [^{18}F]DOPA was obviously higher than that of the remaining pancreatic tissue. Conversely, when the uptake was nearly uniform, the result was considered to represent a diffuse lesion.

In addition to the simple visual inspection, we also employed an objective index of [^{18}F]DOPA uptake termed the 'Pancreas Percentage'. The whole pancreas was first divided into three regions of interest: the head, body and tail. The standardized uptake value (SUV) of each region was then measured 30 min after [^{18}F]DOPA injection. The SUV of the region with the greatest uptake was defined as 100%. The values for the remaining regions were then expressed as percentages compared to that of the region with the greatest uptake. When the Pancreas Percentage of any region was >70% and the SUV was >2·5, the region was considered to be a lesion. For example, when all regions met the criteria, the PET scan was assumed to show diffuse uptake. Similarly, when a single region met the criteria, it was considered to represent a single focal region.

Molecular diagnosis

Prior to the PET studies, all patients received a molecular diagnosis of K_{ATP} channel hyperinsulinism. The methodological details and part of the results of the mutational analyses have been described previously.[7] Briefly, all exons, exon–intron boundaries, and the promoter region of the K_{ATP} channel genes, *ABCC8* and *KCNJ11*, were amplified from genomic DNA and directly sequenced. The parental origin of each mutation was determined by an analysis of the parents. Molecular diagnoses of diffuse and possible focal forms were made on the basis of biallelic and paternally inherited monoallelic K_{ATP} channel mutations, respectively.[7]

Arterial stimulation venous sampling analysis

Arterial stimulation venous sampling (ASVS) analysis was performed under general anaesthesia. All medical treatments were halted 2 days before examination. During the study, normoglycaemia was maintained by glucose infusion. A catheter was placed in the right hepatic vein for sampling. After selective catheterization of the superior mesenteric, gastroduodenal, and splenic arteries, calcium gluconate (0·0125 mmol/kg) was rapidly injected through the catheter in each selectively catheterized artery. Hepatic venous blood was obtained before and 30, 60, 90, 120 and 150 s after calcium injection. A positive finding was defined as a twofold increase in insulin levels in the 30- or 60-s samples (or both) obtained from the hepatic vein.

Results

The patient profiles and results of the [^{18}F]DOPA PET analyses, molecular analyses, ASVS and histological findings are summarized in Table 1.

By inspection, four patients were found to have single focal uptake (patients 4, 5, 6 and 13) and four others were found to have diffuse uptake (patients 1, 2, 3 and 17). We unexpectedly encountered difficulties in assigning the other patients as having diffuse or focal forms. One patient (patient 9) appeared to have no uptake, while others showed irregular uptakes with a variety of background uptakes resembling double focal (patients 7, 8 and 10) or irregular diffuse uptake (patients 11, 12, 14, 15 and 16). Overall, by inspection, the PET diagnosis was consistent with the molecular diagnosis in only 7 of 17 patients. Representative results of these PET scans are shown in Fig. 1.

As it appears that higher background uptake, especially in the head, makes the interpretation of PET scans more difficult, we employed an objective index—the Pancreas Percentage—and reanalysed the PET results. The idea was to smooth out the irregular background uptake and identify the focal lesion with the highest uptake, assuming that multiple focal lesions are extremely rare. Cut-off values were set by taking into account the PET images of patients with known diffuse lesions. When using the Pancreas Percentage, the PET diagnosis was more strongly correlated with the molecular diagnosis; it was consistent in 10 of 17 patients.

Pancreatectomy was performed in 12 patients who exhibited resistance to medical treatment. For patients with paternal mutations, partial resection of the pancreas was attempted using extensive intra-operative biopsies guided by the PET results. In patient 9, who showed no uptake by PET, extreme intensification of PET signals revealed faint uptake in the head (Fig. 1, f2). During surgery, the corresponding area of the pancreas was repeatedly biopsied, which lead to the identification and resection of a thin lesion that was 6 mm in diameter.

Postoperative histology revealed that the molecular diagnosis correctly predicted the histology in all cases. PET diagnosis by inspection was correct in only 6 of 12 cases, whereas the diagnosis was correct in 9 of 12 cases when the Pancreas Percentage was used. Excluding patient 9 whose lesion was initially not visible, two patients (patients 11 and 12) were incorrectly diagnosed using the Pancreas Percentage; histology showed that these two patients had large and somewhat scattered lesions. The diagnosis of the focal form was made through the identification of a region of the pancreas with normal islets. Patient 11 exhibited loss of heterozygosity according to molecular analysis.[7]

Discussion

The present study is the first to report the diagnostic accuracy of [^{18}F]DOPA PET for Asian patients with congenital K_{ATP} channel hyperinsulinism. Although the number of patients is relatively small, two important findings were obtained through this study. First, [^{18}F]DOPA PET appears to be less effective for localizing lesions in Asians than that reported by previous studies mainly from European and North American centres.[2,8–11] Second, the diagnostic accuracy improved substantially (reaching 75%, 9/12) when a quantitative index, the Pancreas Percentage, was employed to analyse the PET results. Three patients were erroneously diagnosed using the Pancreas Percentage; one presented with a lesion

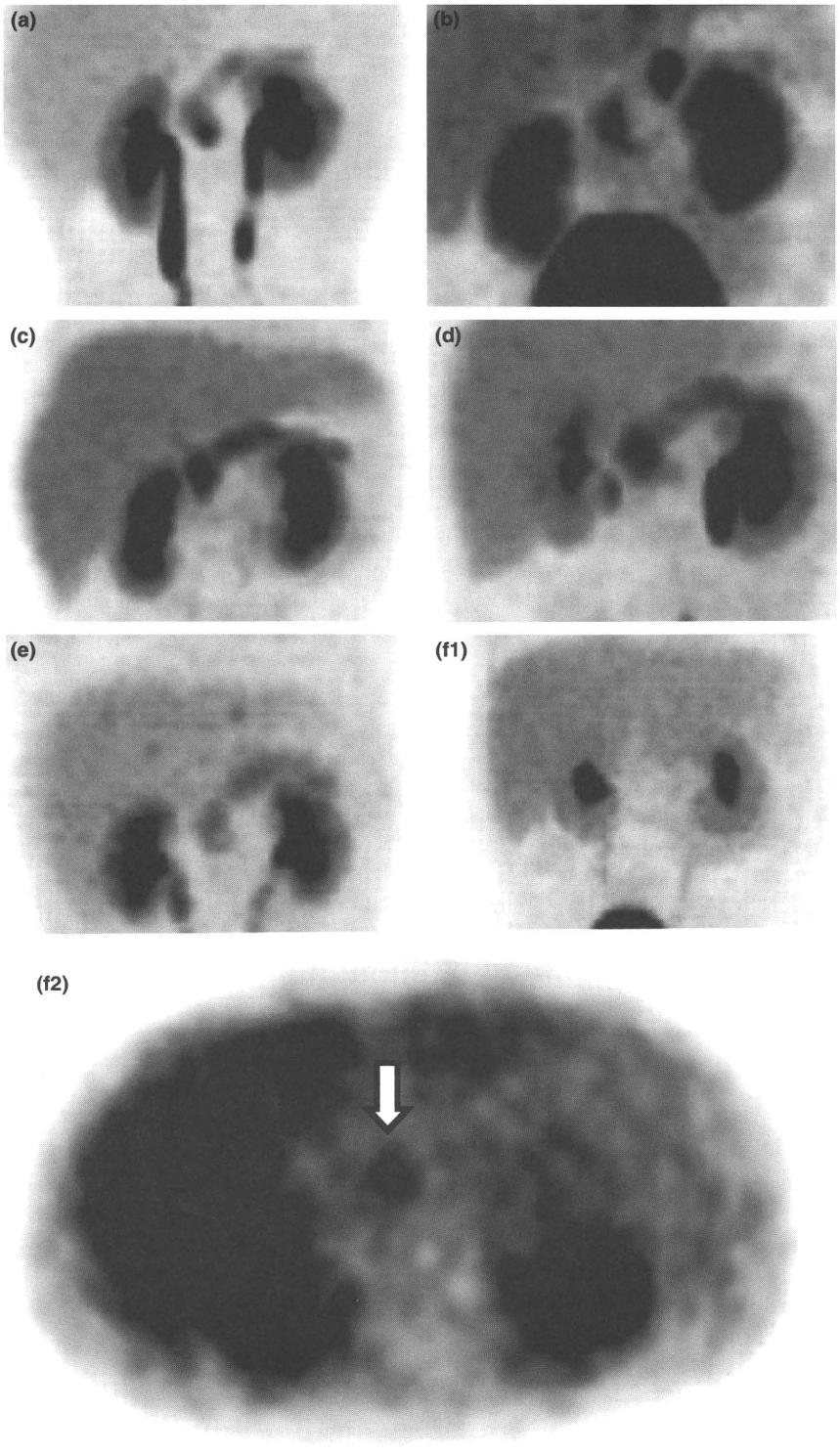

Fig. 1 Representative patterns of [^{18}F]DOPA uptake. Maximum intensity projection (a–f1) and axial image (F2) obtained 30 min after injection. (a, Patient 4): a single focal uptake in the pancreatic head with paternal mutation; histologically, it was a pancreatic head lesion; (b, patient 8): irregular uptake in the pancreatic head and body with a paternal mutation; histologically, it was a pancreatic body lesion (the uptake in the head was false positive); (c, patient 1): typically diffuse uptake with biparental mutations; histologically, it was a diffuse lesion; (d, patient 11): irregular diffuse uptake with a paternal mutation; histologically, it was a large focal lesion (the uptake in the pancreatic head was false positive); (e, patient 12): irregular diffuse uptake with a paternal mutation; histologically, it was a large focal lesion; (f1, patient 9): no uptake with a paternal mutation; histologically, it was a thin lesion in the pancreatic head; (f2, patient 9): retrospective axial imaging revealed weak uptake in the pancreatic head (white arrow). DOPA, dihydroxyphenylalanine.

that was probably smaller and thinner than the detection limits of this methodology. Otonkoski *et al.*[9] report that the smallest focal lesion detected using [^{18}F]DOPA PET is 4 × 5 mm. Likewise, Hardy *et al.*[10] report that the minimum size of focal adenomatosis that can be recognized by [^{18}F]DOPA PET scans is 6 ± 2 mm. In the present study, the smallest lesion detected was 8 mm (patient 4). The other two patients who were erroneously diagnosed as having the diffuse form actually had large focal lesions, which are inherently difficult to differentiate from the diffuse form.

The reason why we observed an increased incidence of irregular appearances on PET scans remains unclear; one possibility is simply a lack of experience. The first [^{18}F]DOPA PET scan for congenital hyperinsulinism in Japan was performed in 2005. Since then, all scans in this country have been performed by our group. In spite of

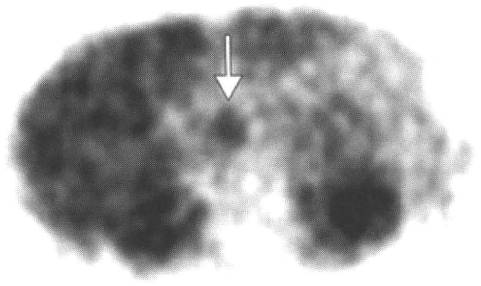

Fig. 2 xxxxxx.

this, our experience is limited as compared with those of large centres in the US and in Europe. Furthermore, correct interpretation might require more experience in this particular imaging technique, even for experienced nuclear radiologists. The use of the Pancreas Percentage might counteract this lack of experience. However, another possibility is the actual biological differences in this disease in Japanese patients. For unknown reasons, our subjects had a relatively large amount of paternally inherited monoallelic mutations as compared with those documented in previous reports.[2,8] This is not caused by a bias at the level of referral to the PET studies. Prior to the PET studies, 16 of the 17 patients underwent a molecular testing in our laboratory which is currently the only facility routinely offering a molecular diagnosis of this disorder in Japan. During the period of this study, we diagnosed five additional cases of K_{ATP} channel hyperinsulinism who did not participate in the PET study; only one of them had biallelic mutations, whereas the other four had paternally inherited monoallelic mutations (data not shown). In addition to the excess of paternally inherited mutations, it appears that many of the patients presented with the less severe phenotype. As shown in Table 1, even with known K_{ATP} channel hyperinsulinism, 5 of 17 patients could be medically treated and patients who underwent surgery could be treated by octreotide at least for some time. Only two of the patients received pancreatectomy within the first 4 months. These milder phenotypes might be correlated with less clear uptake, making PET diagnosis more difficult.

Interestingly, in our series, molecular diagnosis predicted histology most accurately. In contrast to our experience, previous papers report that some patients with paternally inherited monoallelic K_{ATP} channel mutations have a diffuse histology.[2,12] This phenomenon can be partially explained by additional undetected mutations in the maternal allele.[12] However, this speculation does not explain the excess of paternal mutations exhibited by these patients, which is common in previous reports. As preferential underdetection of maternally inherited mutations is unlikely, some of the 'diffuse' forms reported in these publications might actually be large focal lesions with scattered islets, as reported by Yorifuji *et al.*[7]

In summary, in our experience, the diagnostic accuracy of [^{18}F]DOPA PET for congenital hyperinsulinism in Japanese subjects is not as high as that previously reported for Caucasian patients. Preoperative diagnosis of this disorder in Asian subjects should preferably be performed in combination with other diagnostic modalities, especially molecular diagnosis. Nonetheless, [^{18}F]DOPA PET is an indispensable methodology that can accurately localize focal lesions in a noninvasive manner. When combined with the Pancreas Percentage, the diagnostic accuracy of [^{18}F]-fluoro-L-dihydroxyphenylalanine positron emission tomography is augmented, even in Japanese subjects.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (Research on Measures for Intractable Diseases 2009-189 and 2010-101) from the Ministry of Health, Labour, and Welfare of Japan.

Conflicting interests and financial disclosure

Nothing to declare.

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Lasting 18F-DOPA PET uptake after clinical remission of the focal form of congenital hyperinsulinism.

Short title: Spontaneous resolution of congenital hyperinsulinism

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Keywords: congenital hyperinsulinism, hypoglycemia, glucose, [18F]DOPA

Established facts.

- 18F-DOPA PET is a useful tool for detecting the localization of the focal form of KATP channel hyperinsulinism.
- KATP channel hyperinsulinism occasionally resolves itself spontaneously, which has been attributed to the apoptotic death of abnormal β cells in previous studies.

Novel insights.

- Uptake of 18F-DOPA does not always correlate with the insulin-secreting capacity of β cells.
- Spontaneous resolution could be a functional process rather than the result of the apoptotic death of abnormal β cells.

Abstract

Background: Positron emission tomography (PET) using 18F-DOPA is a useful tool for detecting the focal forms of congenital hyperinsulinism. 18F-DOPA is taken up by aromatic L-amino acid decarboxylase in pancreatic β cells. However, the role of this enzyme in insulin secretion is unknown.

Subjects and Methods: A Japanese boy who presented with symptomatic hyperinsulinemic hypoglycemia at the age of 2 days and spontaneous resolution at 1 year 10 months was subjected to mutational analysis and repeated 18F-DOPA PET scans.

Results: Mutational analysis revealed a paternally-inherited monoallelic mutation, c.4186G>T (p.D1396Y), in the *ABCC8* gene, and an 18F-DOPA PET scan revealed focal uptake in the body of the pancreas. The patient was successfully treated with frequent feeding. A follow-up PET scan revealed virtually identical uptake to that observed previously. However, in the arterial stimulation-venous sampling procedure, no significant insulin release was observed. He was placed on a normal diet, and no hypoglycemia recurrence was observed.

Conclusion: This case demonstrates two important findings. Firstly, the uptake of 18F-DOPA does not correlate with the insulin-secreting capacity of the lesion. Secondly, clinical remission could be a functional process not necessarily accompanied by the apoptotic death of abnormal β cells.

Introduction

Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in the neonatal/infantile period. Since severely affected patients often develop profound neurological sequelae (1, 2), surgical resection of the pancreas is mandated when medical treatment is not effective. Regarding surgical treatment, it is critically important to differentiate between the two histological forms of the disorder, the diffuse and focal forms. To surgically treat the diffuse form, subtotal pancreatectomy is indicated. However, the result of this procedure is often not satisfactory, and many patients suffer residual hypoglycemia or develop diabetes mellitus postoperatively (3). On the contrary, patients with the focal form can be cured by partial resection of the pancreas without complications (4, 5).

The focal form is known to occur in individuals with a monoallelic, paternally-inherited mutation in the *ABCC8* or *KCNJ11* gene, which code for the two subunits of the ATP-sensitive potassium channel (K_{ATP} channel) (4). Several diagnostic modalities have been developed to identify focal lesions preoperatively including mutational analysis, the arterial stimulation-venous sampling (ASVS) procedure, pancreatic venous blood sampling (PVS), and positron emission tomography using [18F]-fluoro-L-DOPA (18F-DOPA PET). Currently, 18F-DOPA PET is becoming the modality of choice due to its noninvasiveness and accuracy (6-11). However, in this report, we present a patient with the focal form of congenital hyperinsulinism, in whom disease activity did not correlate with 18F-DOPA uptake.

Case report

The patient was a Japanese boy born after 39 weeks of uneventful pregnancy with a birth weight of 3630 g. There was no family history of hypoglycemia or diabetes mellitus. On day 2, he presented with generalized convulsions accompanied by hypoglycemia (14 mg/dL, 0.78 mmol/L). A subsequent laboratory examination revealed hypoglycemia (39 mg/dL, 2.15 mmol/L) in the presence of an elevated serum insulin level (29.1 μ U/mL, 202 pmol/L), and the peak glucose infusion rate to maintain normoglycemia was 10 mg/kg/min. Otherwise, endocrinological and metabolic screening did not reveal any abnormalities. A diagnosis of congenital hyperinsulinism was made, and mutational analysis using DNA extracted from peripheral blood leukocytes revealed a paternally-inherited heterozygous mutation, c.4186G>T (p.D1396Y), in the *ABCC8* gene. Although functional studies were lacking, this mutation appeared to be pathogenic since it was not listed in the dbSNP (build 13.2, http://www.ncbi.nlm.nih.gov/snp/) and the Japanese SNP (JSNP,

http://snp.ims.u-tokyo.ac.jp/) databases, and both the SIFT (http://sift.bii.a-star.edu.sg/) and the PolyPhen-2 (http://genetics.bwh.harvard.edu/pph/index.html) programs predicted a detrimental effect of this mutation. In addition, the mutation was not found in 106 control Japanese subjects (data not shown). No other mutations were identified in the *KCNJ11*, *GCK*, or *GLUD1* genes. 18F-DOPA PET revealed strong focal uptake in the body of the pancreas, leading to a diagnosis of the focal form of KATP-channel hyperinsulinism (Figure, left panels).

Treatment with 15 mg/kg diazoxide was not effective at preventing hypoglycemia. Since the patient remained free of symptoms due to frequent feeding (10-12 times a day), despite occasional hypoglycemia (< 40 mg/dL, 2.22 mmol/L), he was treated conservatively under frequent self-monitoring of blood glucose.

As the patient remained symptom-free, and self-monitored blood glucose had gradually progressed towards normoglycemia, he underwent a follow-up PET scan at the age of 1 year 10 months. The uptake in the body of the pancreas was virtually identical to that observed in the previous PET scan (Figure, right panels). To investigate the discrepancy between the PET results and clinical improvement, an arterial stimulation venous sampling (ASVS) study was performed, which revealed low basal and stimulated insulin secretion following calcium infusion into the splenic, gastroduodenal, or superior mesenteric arteries (Table). Due to these results, he was placed on a normal diet involving three meals a day, and no further hypoglycemia was observed on frequent blood glucose monitoring. Blood glucose after 12-hour fast constantly remained within a range of 76 - 98 mg/dL (4.21-5.44 mmol/L).

Mutational analysis

Mutational analysis was performed as described previously (12). Briefly, all exons and the exon-intron boundaries of the *KCNJ11*, *ABCC8*, and *GCK* genes were amplified from leukocyte genomic DNA. Then, the amplified products were purified using the Wizard PCR Preps DNA purification system (Promega, WI) and directly sequenced using the BigDye Terminator ver 3.1 Cycle Sequencing Kit (Applied Biosystems, CA). For the *GLUD1* gene, only exons 6-7 (the antenna domain) and 10-12 (the GTP binding domain) were sequenced since the previously reported mutations were exclusively found in these regions. In addition, 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 using the SALSA MLPA kit P117 (MRC Holland, Amsterdam).

Arterial stimulation-venous sampling (ASVS) procedure

The ASVS study was performed as described by Abernethy et al. (13). Briefly, a sampling catheter was inserted from the femoral vein of the infant and placed into the right hepatic vein. Then, another catheter was inserted from the femoral artery and sequentially placed into the splenic, gastroduodenal, and the superior mesenteric arteries, and in each artery, calcium gluconate (0.0125 mmol of calcium per kilogram body weight) diluted in 2 mL of saline were infused over 10 seconds. Blood samples were collected at 30-second intervals for 150 seconds, and the concentrations of calcium, insulin, and glucose were determined for each sample.

[18F]-fluoro- L -DOPA positron emission tomography

18F-DOPA PET studies were performed at the PET facility of Kizawa Memorial Hospital, as described by Ribeiro et al. (10). The scan results were fused with those of a CT scan taken at the same time in order to localize the focal lesion more accurately. Currently, Kizawa Memorial Hospital is the only facility in Japan performing 18F-DOPA PET for congenital hyperinsulinism. All PET results were interpreted by one of the authors, H.N., who is a board certified radiologist with a personal experience of over 7000 PET studies including 28 with 18F-DOPA.

Discussion

In this paper, we report on a patient with the focal form of congenital hyperinsulinism whose focal uptake on 18F-DOPA PET remained virtually unchanged despite clinical remission of hypoglycemia. As the routine clinical practice, the lesion should have been resected immediately following the first PET scan to avoid the risk of possible brain damage. For this particular patient, however, we continued the diet therapy until clinical remission. As a result, this case highlighted two important findings. Firstly, the uptake of 18F-DOPA does not correlate with the insulin-secreting capacity of the lesion, and secondly, clinical remission is probably not caused by the apoptotic death of insulin-producing cells.

The diagnostic usefulness of 18F-DOPA PET for congenital hyperinsulinism was first reported by Ribeiro and Otonkoski for a small number of patients (6, 7). Subsequently, studies with large numbers of patients in Europe and the United States confirmed its usefulness for the differentiation and localization of focal lesions (8-11) and so it is currently widely used for this disorder.

DOPA is taken up by β cells and converted to dopamine by aromatic L-amino acid decarboxylase (AADC) (8). Although β cells display high AADC activity, the role of this enzyme in insulin secretion remains obscure. Using a mouse model, Ericson et al. showed that intravenously injected L-DOPA accumulates within β cell secretory granules and inhibits insulin secretion (14). Also in a mouse model, Lindquist et al. (15) demonstrated that intravenously administered L-DOPA is rapidly converted to

dopamine and inhibited glucose-induced insulin secretion from β cells. The inhibition was reversed with an AADC inhibitor suggesting that dopamine and not DOPA is responsible for this inhibition (15). On the contrary, de Lonlay et al. demonstrated that insulin secretion in a patient with congenital hyperinsulinism was not affected by the administration of an AADC inhibitor (8). An in vitro study using rat INS cells also suggested that insulin secretion is not affected by AADC inhibitor treatment (8). In addition, in adult patients with insulinoma, 18F-DOPA PET could not sensitively detect tumors suggesting that DOPA uptake is not directly related to the insulin secreting capacity of the cells (16). The fact that DOPA uptake by the focal lesion remained virtually identical despite clinical resolution also suggests that the role of AADC in insulin secretion, if any, is relatively small.

It is known that congenital hyperinsulinism is often resolved spontaneously as the patient grows older. The time to resolution differs from case to case; it occurs most often between 1-5 years of age but can happen as early as 8 weeks, even in cases of diffuse form hyperinsulinism caused by biallelic mutations in the KATP channel genes (17). The mechanism leading to spontaneous resolution remains unclear. The apoptotic death of insulin-oversecreting β cells has been proposed as a possible mechanism (18, 19). However, our case showed that, at least in the initial stages, clinical resolution occurs without the death of the causative β cells. Since our case suggests that abnormal β cells lose their responsiveness to calcium, this functional-shut down could be caused by a decrease in the number of functional KATP channels, as is seen in MIN6 cells that have been chronically treated with sulfonylurea (20). Physiologically, spontaneous resolution of KATP-channel hyperinsulinism resembles the phenomenon of β cell failure following prolonged sulfonylurea treatment of patients with diabetes mellitus. Interestingly, it has been reported that the loss of insulin secretory capacity following prolonged glibenclamide treatment is initially functional and reversible although the eventual result is known to be the absolute loss of β cell mass (21). Similar sequence of events might be operating behind the spontaneous resolution of congenital hyperinsulinism. Understanding the mechanism of the spontaneous resolution of this condition might lead to an efficient medical therapy if we could manipulate the process.

Acknowledgement

We thank Seisuke Fukuyama at Kizawa Memorial Hospital for helping us to obtain appropriate PET images. This work was supported by a Grant-in-Aid for Scientific Research (Research on Measures for Intractable Diseases 2010-101) from the Ministry of Health, Labour, and Welfare of Japan.

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Figure legend

18F-DOPA PET scans taken at 8 months (left) and 1 year 10 months (right). Upper panels show coronal images of abdominal PET scans and lower panels show fused axial PET/CT images. The maximal standardized uptake values (SUV) for these lesions were 5.0 (left) and 6.8 (right), respectively.

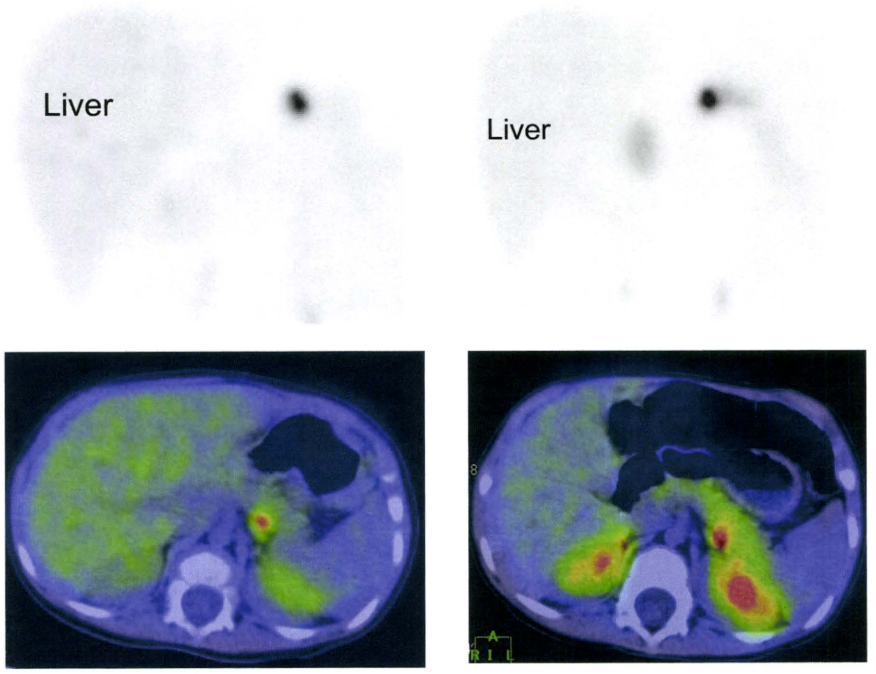

Table Results of the arterial stimulation-venous sampling (ASVS) procedure.

	Insulin (μU/mL)		
Time (sec)	splenic	gastroduodenal	superior mesenteric
0	6.2	5.0	4.7
30	5.2	5.0	8.2
60	6.9	8.2	5.8
90	7.6	9.9	7.7
120	5.2	7.7	3.7

特集　小児の輸液ベーシックガイド

Ⅱ．各　論

低血糖

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要旨

低血糖（小児では血糖値＜45 mg/dL）はけいれん・意識障害につながるため，緊急に対応すべき状態である．しかしながら，その後の対応のためには病因を明らかにすることも重要である．発症状況の詳細な聴取，ブドウ糖投与前に行う採血・採尿検査，初期ブドウ糖投与後の維持療法に対する血糖値の推移などが病因診断の重要な材料となる．漫然とした糖投与を行うことのないよう注意すべきである．

Key words　低血糖，グルコース，先天代謝異常

はじめに

「低血糖」は，脱水やその他の水・電解質異常と並んで，臨床医が輸液療法を考えるおもな体液異常のひとつである．しかしながら現実には，低血糖→高張ブドウ糖液のワンショット静注→血糖値が戻っていれば高濃度ブドウ糖の維持輸液でしばらく経過観察し，再度，低下がなければ空腹を避けるように指導して帰宅，といったグルコースホメオスタシスをあまり考慮しない輸液療法が行われることが多いのが現状である．もう少し計画的な輸液を行うことで低血糖をより有効に治療し，さらに低血糖の原因検索にも多くの情報を与えてくれることを本稿で伝えたい．

血糖維持の重要性

「血糖」の役割は，各組織へのブドウ糖の供給である．すべての組織はATPの産生を必要とするが，とりわけ脳はそのATP源をブドウ糖とケトン体に依存している．飢餓時においても，脳のATPのおよそ50%はブドウ糖に依存しており，ケトン体だけでは維持できない．また，筋や肝と異なり脳ではグリコーゲンなどの形でのブドウ糖貯蔵がなく，実際に成人では，全身の2%の重量しかない脳が全身で用いるブドウ糖のうち20%を使用しているといわれる．それに対して筋や心筋は，ケトン体と脂肪酸を有効に使用できる．したがって，低血糖に際してもっとも影響を受けるのは脳である．低血糖に伴う症状も多くは脳のエネルギー欠乏に起因する．

低血糖の定義

低血糖の定義はさまざまで，真にエビデンスに基づく定義は存在しない．しかしながら，成人で血糖値3 mmol/L（54 mg/dL）以下，小児で2.5 mmol/L（45 mg/dL）以下が一般によく用いられる．一方，糖尿病診療などの場面では70 mg/dL以下を低血糖として扱うことが多い．糖尿病関連の低血糖症は大部分がインスリン過剰によるもので，グリコーゲン分解や糖新生などの血糖上昇機構が

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抑制されるため高度の低血糖に陥りやすいことを考慮すると，この定義は現実的であるといえる．しかしながら，低血糖の診断のための，いわゆる“critical sample”採取の条件としては，70 mg/dLを下回っただけでは判然とした結果が得られないことが多い．

低血糖の原因

ヒトの血糖維持機構は，①食事による血糖上昇，②肝グリコーゲンの分解によるブドウ糖の産生，③糖新生系によるピルビン酸を起点とするグルコースの産生，の3種の血糖上昇機構が，インスリンによる血糖降下作用と拮抗して一定の狭い範囲内の血糖値を維持している（図1，図2）[3]．食事の消化吸収による血糖上昇は通常，食後4時間程度，授乳中の乳児で3時間程度しかもたない．その後は，肝からのグリコーゲン分解による血糖維持が続き，食後16時間前後からは糖新生系による血糖維持に依存する．

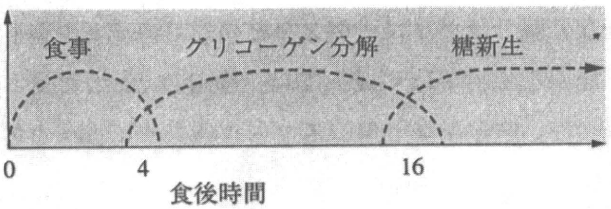

図1　食後血糖の維持機構

低血糖症は，血糖上昇機構の破綻ないし血糖低下機構の亢進により発症する[1]．血糖上昇機構の破綻による低血糖症は前述の血糖維持における役割分担に対応して，機序別に食後一定の時間帯に症状が出ることが多い．すなわち，糖原病などのグリコーゲン分解異常に基づく低血糖症や脂肪酸β酸化異常症，糖新生系の異常症などは，食後一定の時間が経過しないと発症してこない．したがって出生直後を除くと，離乳期に入って食事間隔が空いてくるまでは，これらの原因による低血糖は発症しない．これに対し，血糖低下機構の亢進による場合（高インスリン血症など）は食後時間にかかわらず症状を呈する．空腹時に発症するとは限らず，ダンピング症候群のように食後2時間前後で発症することもある．すなわち，新生児持続性低血糖症のもっとも多い原因は先天性高インスリン血症である[2]．既知の低血糖の原因疾患を表1[3]にあげる．

血糖上昇機構の破綻による低血糖症

食事による血糖上昇の破綻によってひきおこされる低血糖症は通常，消化管疾患など臨床的に明らかである．グリコーゲン分解の異常による低血糖症は典型的には肝型糖原病であるが，重症肝疾患や低出生体重児，あるいはグリコーゲン合成酵

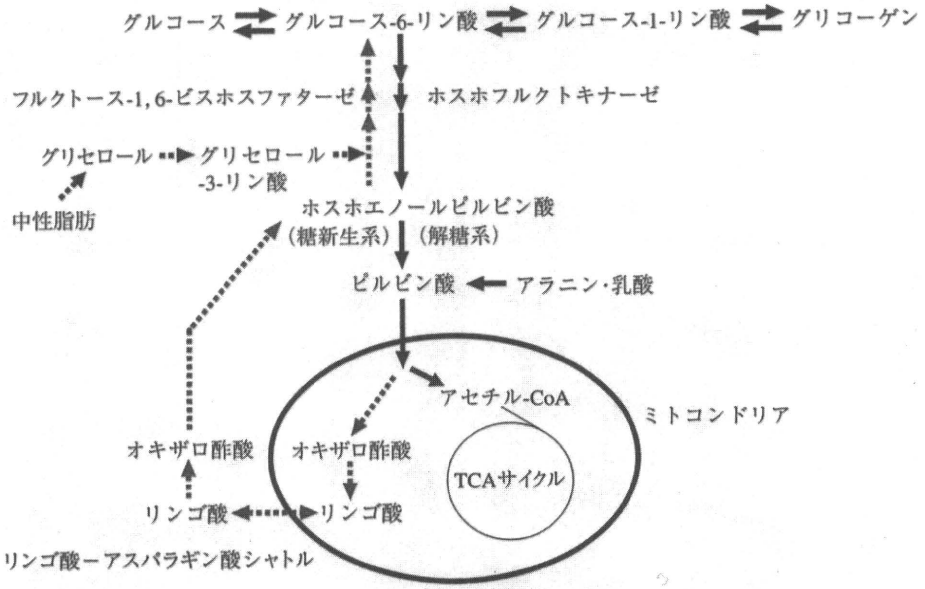

図2　グリコーゲン分解系と糖新生系（文献3）より引用，一部改変）

素異常症（糖原病0型）などでも肝グリコーゲンが枯渇するため，グリコーゲン分解によるグルコース産生の低下をきたす．すなわち，グルカゴン負荷による血糖上昇がみられない．

糖新生系は，図2[3]に示すようにピルビン酸を起点とするブドウ糖産生の機構である．ピルビン酸はmetabolic sinkともいわれ，血中に蓄積せず乳酸，アラニンへと代謝される．すなわち，糖新生が必要な状態ではアラニン，乳酸を材料として糖新生系でグルコースを合成する．大部分は解糖系の逆戻りであるが，一部，糖新生系特有の酵素を使用しており，これらの酵素の欠損症で遺伝性糖新生異常を生じる．また，中性脂肪の加水分解により生じたグリセロールがグリセロールキナーゼを介して合流しているため，同酵素異常でも糖新生機能低下による低血糖を示す．しかしながら，こういった糖新生系固有の酵素異常による低血糖症の頻度は高くなく，フルクトース-1,6-ビスホスファターゼ欠損症，グリセロールキナーゼ欠損症以外は非常にまれである．

脂肪酸のβ酸化からグルコースを産生する経路はヒトでは存在しないが，β酸化系の最終産物であるアセチル-CoAは糖新生系酵素のアクチベータであるため，β酸化異常症やカルニチン代謝異常症では糖新生異常と臨床的に似かよった低血糖症をきたす．食事性やピボキシル基を有する抗菌薬の長期連用による二次性カルニチン欠乏も同様に，臨床的には糖新生異常として表現される．また，いわゆる“ケトン性低血糖症”も糖新生系の未熟によるものと考えられている．

特記すべきは，新生児期直接ビリルビン優位の黄疸の原因の一つであるシトリン欠損症〔新生児肝内胆汁うっ滞症（neonatal intrahepatic cholestasis caused by citrin deficiency:NICCD)〕である．シトリンは糖新生系において，ミトコンドリア内のリンゴ酸を細胞質に輸送するために必要なリンゴ酸－アスパラギン酸シャトルと共役するaspartate glutamate carrier(AGC)の活性をもっている．その欠損によりリンゴ酸－アスパラギン酸シャトルが障害されると，臨床的に糖新生異常としての低血糖をきたす．

表1　低血糖の原因疾患（文献3）より引用，一部改変）

疾患群	疾患（疾患群）
高インスリン血症・拮抗ホルモン欠損症	高インスリン血症 拮抗ホルモン異常症 ・汎下垂体機能低下症 ・副腎皮質機能低下症 ・グルカゴン欠損症
糖代謝異常による反応性低血糖症	ガラクトース血症（乳糖摂取時） フルクトース不耐症（果糖摂取時）
グリコーゲン分解の異常	糖原病 Ⅰa:glucose 6-phosphatase Ⅰb:glucose 6-phosphate translocase Ⅲ：debranching enzyme Ⅵ：liver phosphorylase Ⅷ：phosphorylase b kinase Ⅺ：Fanconi-Bickel syndrome, GLUT2 0型：glycogen synthetase
糖新生系異常	糖新生関連酵素異常症 ・フルクトース-1,6-ビスホスファターゼ欠損症 ・ピルビン酸カルボキシラーゼ欠損症 ・ホスホエノールピルビン酸カルボキシキナーゼ ・その他 シトリン欠損症 グリセロールキナーゼ欠損症 ケトン性低血糖症など 脂肪酸酸化異常症 ・脂肪酸β酸化異常症 ・カルニチン代謝異常症 ・ミトコンドリア病 ・二次性カルニチン欠乏症 食事性 抗菌薬（ピボキシル系） 有機酸血症 ・ケトン体産生異常症 3-ヒドロキシ-3-メチルグルタリルCoA（HMG-CoA）リアーゼ欠損症 HMG-CoA合成酵素欠損症

＊SGA（small-for-gestational age）性低血糖症など新生児特有の疾患や肝不全など臨床的に明らかな原因を除く

血糖低下機構の亢進による低血糖症

インスリン過多によるものが大部分である．臨床的にもっとも頻度が高いのは糖尿病治療中のイ

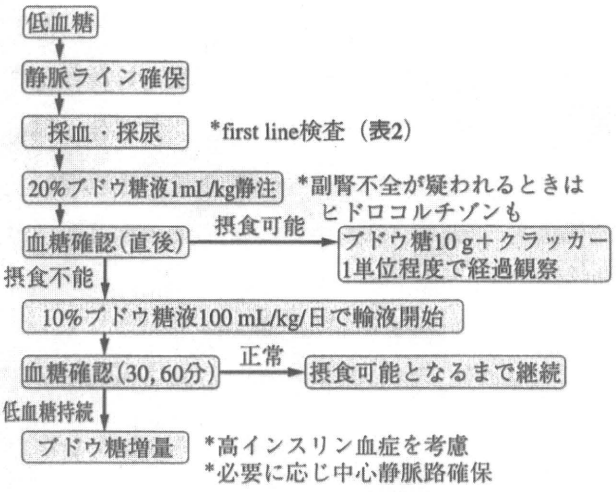

図3　低血糖時の輸液療法
数値は目安であり，患児の状態に応じて適宜変更する

インスリン過多による低血糖であるが，これら医原性のものを除くと，成人ではインスリノーマが多く，小児では先天性高インスリン血症によることが多い．インスリン自己免疫症候群，腫瘍性のbig IGF2による低血糖は成人では比較的多いが，小児期にはまれである．また，ガラクトース血症やフルクトース不耐症の患児が制限糖質を摂取した際に急激な低血糖をきたすことがあるが，機序は不明である．

低血糖時の輸液療法（図3）

原則として，症状を伴う高度の低血糖で食事が摂れない場合は，まずブドウ糖液のワンショット静注を行う．この際，ブドウ糖液のワンショット静注に先立ち，静注のために確保したラインを使用して可能な限り原因鑑別に必要な採血検査を施行する．可能であれば検尿も行う．いわゆるcritical sampleで，原因鑑別に有用である（**表2**）[1]．

循環血液量を80 mL/kgとすると，20%ブドウ糖液を1 mL/kgでワンショット静注すると一時的に200 mg/mLに至る濃度のブドウ糖が静注されることになり，いったん血糖を上昇させるには十分な量である．過量のブドウ糖液静注は高血糖を招くだけではなく，反応性のインスリン分泌により低血糖のリバウンドを招く可能性もある．また，血管刺激性が強いため50%ブドウ糖液を使用することは好ましくない．ワンショット静注を行ったら，直後に血糖の上昇を確認する．

表2　低血糖時に行うべきfirst line検査（critical sample）
文献1）より引用，一部改変

検　体	検査項目
血液	CBC，CRP，血液一般生化学検査，電解質 血糖値 インスリン・Cペプチド 血液ガス分析 遊離脂肪酸 アンモニア 血中ケトン体分画 乳酸・ピルビン酸 副腎皮質刺激ホルモン（ACTH）・コルチゾール FT_4・甲状腺刺激ホルモン（TSH） 成長ホルモン（GH）・インスリン様成長因子-1（IGF1，ソマトメジンC） 血清アシルカルニチンプロフィル（タンデム質量分析計） 血清保存（凍結）
尿	検尿 尿有機酸分析（ジカルボン酸尿など） 尿保存（凍結）

一部症例では病歴から原因の推定が可能な場合がある．たとえば，糖尿病でインスリン治療中であればインスリン過多が推測される．あるいは，脳腫瘍治療後の汎下垂体機能低下症の治療中や先天性副腎過形成で治療中であれば，副腎不全が疑われる．副腎不全では，ブドウ糖液の静注によって血糖値は改善しても状態の改善はなく，ヒドロコルチゾンの同時静注が必要である（新生児・乳児では25～50 mg，幼児50～100 mg，学童以上100～200 mg）．

ワンショット静注により意識清明となり摂食が可能であれば，糖尿病児などに準じてブドウ糖10 g＋クラッカーなどを1単位程度摂らせて経過を観察する．ワンショット静注後も意識の改善がなく摂食不能であれば，引き続きブドウ糖輸液を行う．多くの場合，発症時には原因が不明であるため，まず生理的な肝のブドウ糖産生量に準じた量のブドウ糖液を維持輸液する．同時に輸注する電解質や輸液の総量はもとの病態に応じたもので

差し支えない．持続輸液開始後30分，60分で血糖値を再検する．

安静時，肝でのグルコース産生は成人で2 mg/kg/分前後[4]，成熟新生児で4～6 mg/kg/分前後[5]，小児期にはその中間と考えられている．インスリン過剰による低血糖症でなければ，この程度の輸液で血糖値は維持される．一方，インスリン過剰状態では，これより多くの持続的ブドウ糖輸液が必要となる．病歴から明らかにインスリン過剰による低血糖が疑われる場合は，当初から上記よりも多いブドウ糖注入量が必要である．このことは高インスリン性低血糖症を疑う診断基準の一つにもなっており，治療的診断ともなる．注意を要するのは下垂体機能低下症やグルカゴン欠乏による低血糖症で，これらのインスリン拮抗ホルモン欠損症ではインスリン過剰に類似した病態を示すことがある．末梢静脈からの高濃度ブドウ糖輸液は短時間であってもブドウ糖濃度12%までが上限で，10%でも長時間の輸液はむずかしい．それ以上のブドウ糖濃度が必要な場合は中心静脈路の確保を考慮する．

10%ブドウ糖液100 mL/kg/日で輸液を行うと約7 mg/kg/分のブドウ糖注入率となるので，高インスリン血症以外の原因による低血糖の場合，多くは末梢からの輸液で血糖を維持できることになる．ワンショット静注前に採取したcritical sampleの検査結果が戻るには時間がかかることが多いが，高インスリン血症，脂肪酸β酸化・カルニチン代謝異常症・ケトン体代謝異常を除くと，一般には低血糖時に血中ケトン体が上昇することが多い．Saudubrayら[6]によると，24時間飢餓後の正常小児（4カ月～13歳）ではケトン体値（3-ヒドロキシ酪酸＋アセト酢酸）が1,500 μmol/Lを超え，20時間飢餓後でも多くの場合，1,000 μmol/Lを超える．新生児では一般にケトン体産生能が低いことが知られているが，まったく産生されないわけではない．原因判明までの簡易的対応として尿ケトン体が高度陽性であれば，多くは上記範囲内の

確認問題

問 3歳男児．現在まで特記すべき病歴なし．朝から元気がなく，ボーッとして食事も摂れないため受診．来院時，身体所見に異常なく，身長94 cm，体重14.2 kg，意識状態Japan Coma Scale（JCS）20．緊急検査にてWBC 12,000/mm^3，RBC 395×10^4/mm^3，Hb 11.4 g/dL，PLT 38×10^4/mm^3，Na 143 mEq/L，K 4.2 mEq/L，Ca 10.3 mg/dL，血糖32 mg/dL，AST 23 IU/L，ALT 18 IU/L，CRE 0.3 mg/dL，BUN 18 mg/dL，CRP＜0.3 mg/dL，尿ケトン体4＋であった．

この児に対して正しい治療はどれか．

1）50%ブドウ糖液15 mLをまず静注し，10%ブドウ糖含輸液を100 mL/時で持続投与した

2）50%ブドウ糖液8 mLをまず静注し，10%ブドウ糖含輸液を60 mL/時で持続投与した

3）20%ブドウ糖液15 mLをまず静注し，10%ブドウ糖含輸液を100 mL/時で持続投与した

4）20%ブドウ糖液15 mLをまず静注し，10%ブドウ糖含輸液を60 mL/時で持続投与した

☞ 解答p. 308へ

ブドウ糖輸液で十分である.

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