研究成果の刊行に関する一覧表

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雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
多田裕	発育曲線を未熟児養育支援に活かすために	母子保健	645	10-11	2013
河野由美	ハイリスク児の発達評価法；わが国におけるフォローアップ体制の構築とそのプロダクト	周産期新生児誌	49(1)	109-112	2013
Ishii N, Kono Y, Yonemoto N, et al	Outcomes of Infants Born at 22 and 23 Weeks' Gestation.	Pediatrics	132(1)	62-71	2013
河野由美	長期フォローアップと多種職連携	周産期医学	43(3)	345-348	2013

V．研究成果の刊行物・別冊

◆小児
発育曲線を未熟児養育支援に活かすために

東邦大学名誉教授　多田 裕

昨春、発育調査の新たな結果に基づいて、母子健康手帳の乳幼児身体発育曲線が改訂されました。
未熟児の発育を支援していくとき、新しくなった身体発育曲線をどう生かしていけばよいのか。東邦大学医学部名誉教授で、乳幼児身体発育調査の評価と活用方法に詳しい多田裕先生に解説をお願いしました。

わが国の乳幼児の身体発育は10年ごとに厚生労働省により調査が実施されている。母子健康手帳に掲載されている乳幼児身体発育曲線は、この調査結果に基づいて作成されたものであり、身体発育曲線が10年ごとに改訂されるのに合わせて、母子健康手帳も10年ごとにその他の部分も含めて改訂される。最近の乳幼児身体発育調査は2010年（平成22年）に実施されたので、この調査結果に基づく発育曲線が掲載された新しい母子健康手帳が平成24年4月から使用されるようになった。今後10年間は、この発育曲線を用いた母子健康手帳が交付される。

身体発育曲線の見方

新しい母子健康手帳には、2010年の調査値に基づいて男女・年齢（月齢）別の身長、体重、頭囲の発育曲線が3から97パーセンタイルの幅で色づけられて掲載されている。

また、乳児の身長と体重のバランスを見るためには、身長体重曲線により肥満度が示されている。肥満度（％）は標準体重（幼児の体重と身長との関係を2次式で表した値を基に計算）から、（実測体重（kg）－身長別標準体重（kg）／身長別標準体重）×100で求めることができる。母子健康手帳には、±15％を「ふつう」として帯で示し、＋15％以上＋20％未満を「ふとりぎみ」、＋20％以上＋30％未満を「ややふとりすぎ」、＋30％以上を「ふとりすぎ」、－20％超から－15％以下を「やせ」、－20％以下を「やせすぎ」としてその範囲が線で示されている。従来は乳幼児の身長と体重のバランスの評価にはカウプ指数（体重（g）÷身長（cm）の二乗×10）を用いることが多かったが、カウプ指数は正常範囲が年齢により変化するので、幼児では身長体重曲線で判定する方が適当であるとされている。

乳幼児の発育は経過を追うことが大事

身体計測値は測定の際の誤差やそのときの児の体調によって変化する。児の状態による変化が大きいのは体重、身長、頭囲の順であるが、身長は測定誤差が生じやすいので疑問がある場合には再測定する。体重はその時点の一時的な状態でも変わるので、発育の評価のみでなく、哺乳状態や脱水、浮腫などを明らかにする意義もある。このように測定時の状態や測定上の問題があることもあるので、発育の評価には一時点でなく経過を追って測定しプロットすることが重要である。

母子健康手帳にプロットする場合には3から97パーセンタイルの帯の中に入っていることがひとつの目安になるが、詳細に身体発育の変化を評価するためには、3、10、25、50、75、90、97パーセンタイル値が記入された発育曲線を利用する。この数値や曲線は厚生労働省のホームページ[※1]からダウンロードするか母子保健事業団発行の「乳幼児身体発育値」を参照する。

早産児、低出生体重児の発育をどう評価するか

2010年の幼児身体発育曲線は、一般調査7652人、病院調査4774人の調査結果からはずれ値を除いて計算してある。

今回の調査値を以前の調査の値と比較すると、身長体重ともやや減少している。乳幼児期の身体発育は出生時の体格の影響があるので、今回の調査値の減少は、出生体重に影響を及ぼす在胎期間、多胎、母親の年齢、合併症、非妊時のBMI、妊娠中の栄養摂取状況、喫煙、飲酒など多くの要因が絡んでいると考えられる。このため、個々の子どもの乳幼児期の身体発育を評価する際には、それぞれの子どもの背景を考慮することが必要になる。なかでも、在胎期間は出生時の身体計測値に及ぼす影響が大きい。

修正月齢という考え方

早産で在胎期間が短いうちに出生した児の身体発育の評価には、在胎期間の影響を小さくするために、出産予定日に出生したものとして生後の月齢を計算する修正月齢を用いる。すなわち、母子健康手帳の発育曲線にプロットする際には、出産予定日の測定値を表の0（出生時）のところに印をつけ、以後も月齢を出産予定日からの期間で算定して評価する。

早産児は在胎期間が短いほど出産予定日になっても正期産出生児より身長や体重が少ないことが多いので、前述のパーセンタイル曲線が記入されている発育曲線にプロットし次第に中央値に向かって改善しているかで判断する。経過によってもパーセンタイル曲線に平行または低下している場合には、合併症、栄養、内分泌的な異常がないかを検討する。

※1 http://www.mhlw.go.jp/stf/houdou/2r9852000001t3so.html

運動発達などとの関連

運動発達や精神発達は体格が小さくても修正月齢に従った発育を示す例も多いが、体格が小さいことが影響し発達が遅い例も見られるので、身体発育との関連を見て評価する必要がある。

頭囲は身長、体重に比べて低下がないことが多いが、パーセンタイル曲線をまたいで変化する場合には注意する。なお身体発育曲線のなかに併記されている運動発達の矢印は50%から90%の児ができるようになった月齢の目安なので、早産児では達成できていなくても正常なことが多く、親が過度に心配しないように配慮する。

SGA児について

在胎期間に比較して出生時の身長、体重ともに在胎週数相当の標準より10%以上小さい児はSGA(small for gestational age)児と定義される。

生後は身長が標準偏差の2倍以上低い児は低身長と定義されるが、約90%のSGA児は2歳までに−2SD（−2.3パーセンタイル）以上の標準に改善する。しかし2歳までにキャッチアップしなかった児は低身長で経過

することが多いと報告されている。

SGAで出生し、身長、体重のどちらかが−2SD未満で3歳以降の身長が−2.5SD未満であり、かつ治療前の1年間の成長率がSDスコアで0未満の場合には、希望すればSGA低身長症の成長ホルモン治療の適応となることも知っておく。

集団としての発育の評価

乳幼児の個々の身体発育を評価するには2010年の値を用いることになっているが、集団としての発育を比較する場合には、昨年までの母子健康手帳の発育曲線に用いられていた2000年の調査値を用いることになっている。

この理由としては、日本人成人身長に関するsecular trend（年代間の成長促進現象）は男女とも1990年代後半に終了したと考えられること、日本人の成熟（思春期の時期）に関するsecular trendも2000年にほぼ終了したと考えられること（日本小児内分泌学会、日本成長学会）から、異なる集団の身体発育値を比較する基準が10年ごとに変わるのは適当ではないので、今後は2000年の測定値を基準値として比較することが望ましいと

考えられるからである。したがって、年代、地域、対象の異なる集団などの身体測定値を調査、集計、解析、比較する際の基準の値は2000年の調査値を用いる。

18歳までの成長曲線をどう見るか

母子健康手帳の記載が予防接種の公的記録として就学後にも役立てられるようになったことと、任意様式の部分に18歳までの成長曲線（この曲線の乳児期の発育は2000年の調査値）が載せられているのは、従来と異なり母子健康手帳を学童期以降も継続して用い、成人になるまでの発育を記録できるようになった今回の改訂の新しい点である。
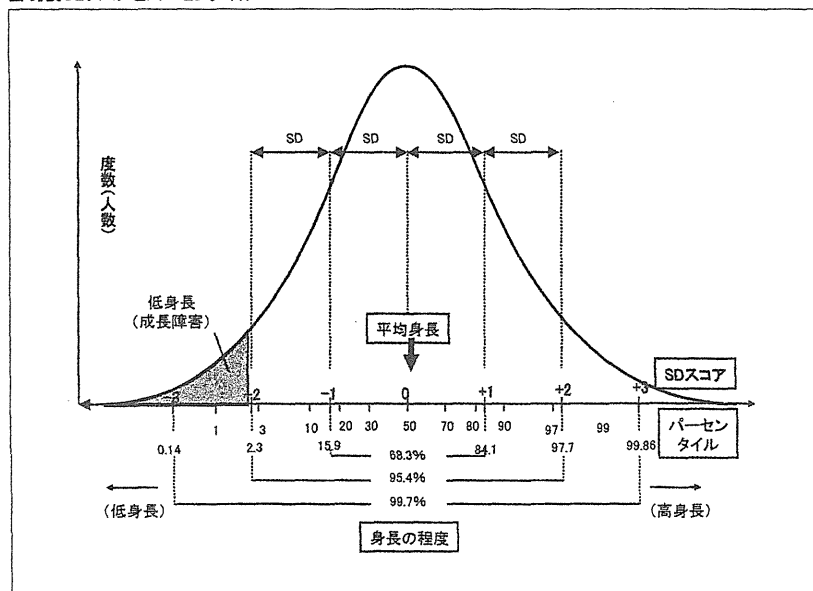
乳幼児発育曲線はパーセンタイル値が用いられているが、学童期以降の発育値は標準偏差（SD）を基準に中央値からの差を見る（SDS:SD Score）ことが多い。パーセンタイルとSDの比較を図に示したので参考にされたい。

「SGA低身長症」の治療適応になる条件

・出生時の身長、体重がともに在胎週数相当の標準より10%以上小さいSGA児であったこと

・出生時の身長、体重のどちらかが−2SD（−2.3パーセンタイル）未満で3歳以降の身長が−2.5SD未満

・以上に加えて、治療前1年間の成長率がSDスコアで0未満で、治療を希望する場合

図 身長SDスコアとパーセンタイル

シンポジウム10「ハイリスク児の発達評価法」

わが国におけるフォローアップ体制の構築とそのプロダクト

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　NICUを退院したハイリスク児の発達評価の目的は，一人一人の子どもの発達の特徴を見出し応じた支援を行うこと，周産期医療のアウトカム指標である発達予後を明らかにし医療の改善をすすめることである．前者は，clinical follow-upの，後者はresearch follow-upの目的でもある．極低出生体重児を中心としたハイリスク児のフォローアップで用いる発達評価検査の条件として，子どもの支援を念頭においたclinical follow-upでは，子どもの全体的な発達と領域別のプロフィールを客観的にとらえることができること，結果をもとに適切な助言ができること，心理士等の専門職者が対面して個別に児を評価することによりその評価を家族にフィードバックすることなどの条件が挙げられる．一方，research follow-upでは，児の知能水準や合併症に大きく影響されることなく実施できること，標準化され一般児と比較できること，さらに多施設共同研究であればデータを集積し分析することが可能な普及した検査法であること，比較対照試験であれば，エビデンスとして受け入れられるグローバルスタンダードな検査であることも挙げられる．

発達検査の実施体制の構築

　全国の周産期センターネットワーク（以下NRN）を形成する「重症新生児のアウトカム改善に関する多施設共同研究」では，フォローアップ体制の構築にあたって，3歳（歴年齢3歳0カ月〜3歳6カ月）で統一の方法でフォローアップを行い，発達評価法として心理士等による新版K式発達検査（K式）の実施をプロトコールとした[1]．ハイリスク児フォローアップ研究会では，その他に修正1歳半でのK式，就学前・小学校3年生でのWISC検査（現在ではWISC-IV）を推奨している[2]．

　統一プロトコールでの3歳フォローアップが可能なNRN施設は，2004年の10施設から2011年の調査では57施設まで増加した．NRNデータベースに登録された2003-2007年出生の極低出生体重児10,394名のうち，3歳予後データは2011年11月末時点で5,761名分が登録された．予後データのある5,761名の発達評価法は，3,833名（66％）がK式，568名（10％）がその他の検査法，371名（6％）が主治医判定によるもので，989名（17％）は評価が欠側していた（図1）．出生年度別にその実数と割合をみると，K式によるものが2003年出生児では583名（63％）であったが，2006年では884名（64％）と実数は増加している．2011年に行ったアンケート調査（52施設の回答）では，すべての施設が1歳半，3歳で個別発達検査を実施し，1歳半で63％，3歳で88％がK式であった．検査実施者は83％が医師以外（心理士，STなど）であった．

新版K式発達検査による極低出生体重児の3歳発達予後

　図2aに2003-2007年出生の極低出生体重児3,831名のK式のDQ値のDQ70未満，DQ70〜84，DQ85以上の割合を在胎週数別に示した．DQ70未満，DQ70〜84の割合は在胎週数が大きくなるほど低下し，在胎32週で最低となり，以後の週数では増加した．在胎33週以降では先天奇形の合併児やSGA児の割合が増えるためと考えられる．一方，在胎22〜24週でのDQ70未満の割合はほぼ同率で評価対象の約1/3が相当した．DQ85以上の割合は，在胎22〜24週は30％未満，在胎27週をこえると50％以上となった．DQ70未満の割合は在胎週数とともに低下するのに対し，DQ70〜84のいわゆるborderlineの割合は，在胎22〜32週まで約30〜40％の同率で認められた．図2bに姿勢・運動，認知・適応，言語・社会の領域別指数の割合を在胎32週以下の対象で週数別に示した．いずれの領域でも在胎期間が小さいほど70未満の割合が高く，言語・社会領域でより強く在胎期間の影響をうけていた．

発達評価からみた予後と周産期医療へのフィードバック

　統一プロトコールによる発達評価により，多施設デ

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図1　NRN 3 歳予後データ登録のある 2003-2007 年出生極低出生体重児 5,761 例の発達評価方法とその結果
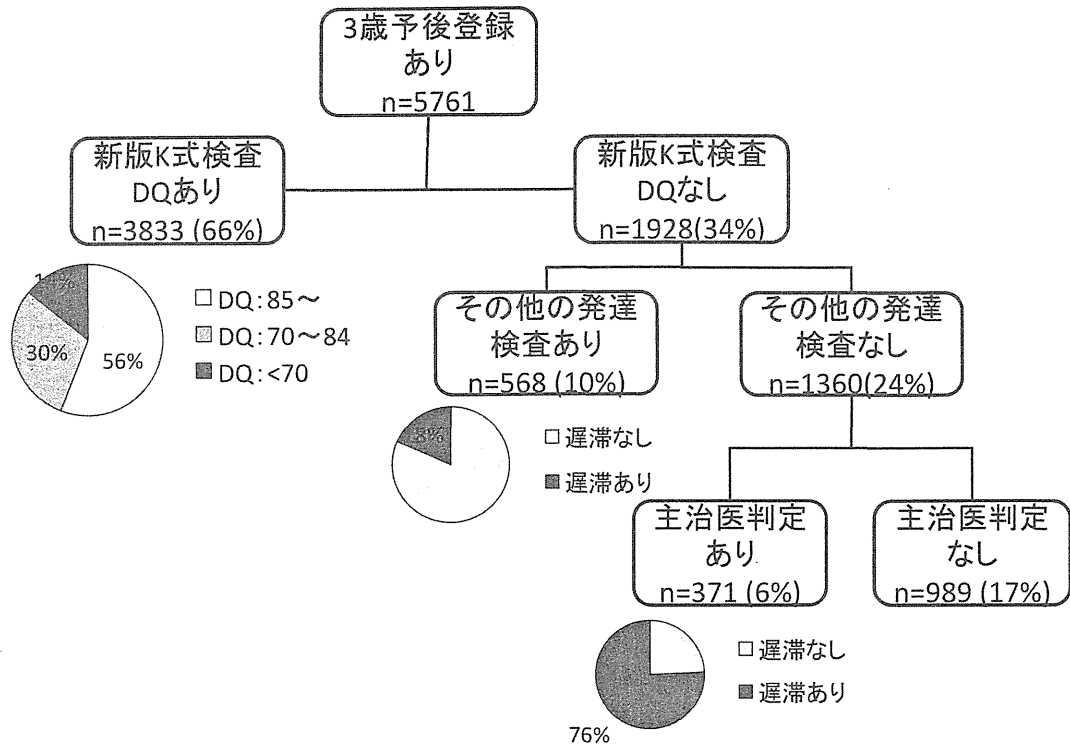
図2　NRN 3 歳予後データ登録 2003-2007 年出生極低出生体重児
a：在胎週数別新版 K 式発達検査発達指数（DQ）評価の割合（n＝3,833）
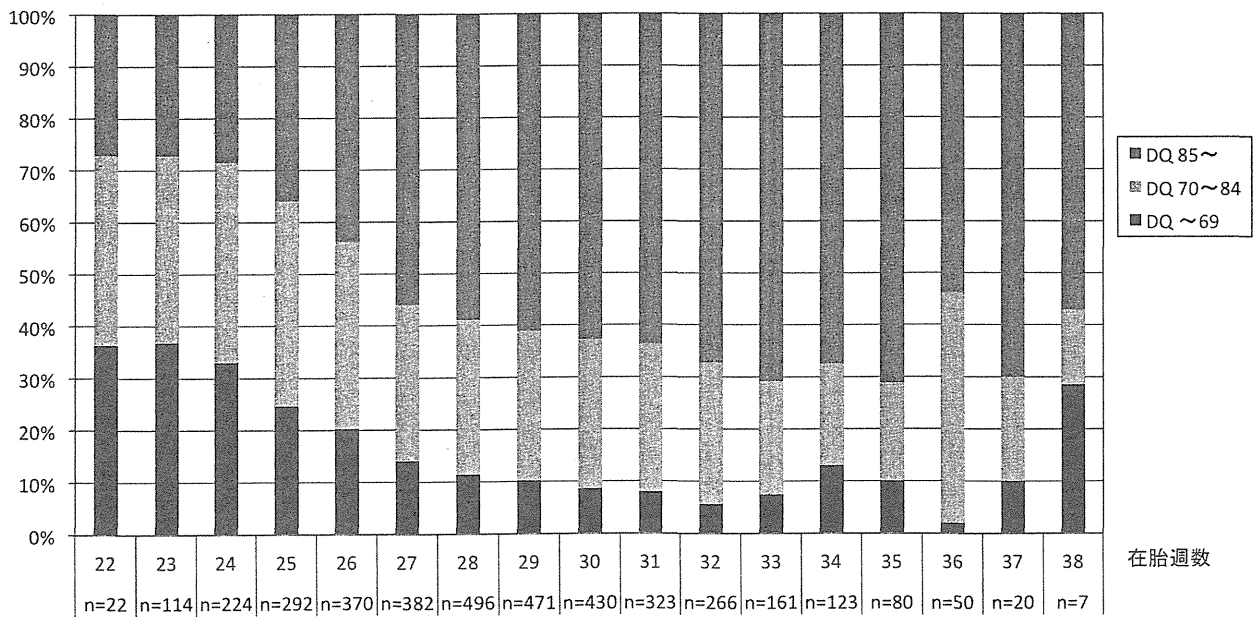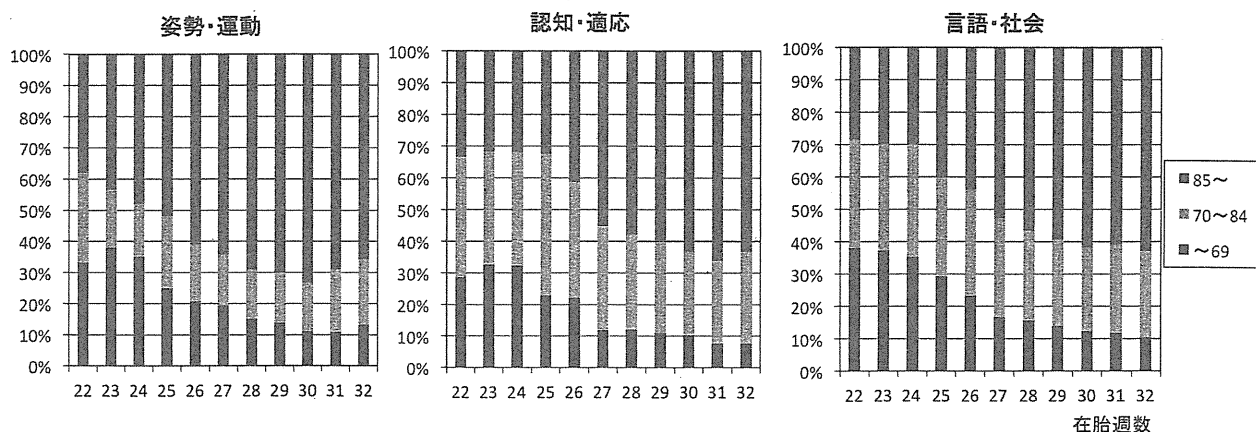
b：在胎33週未満児の在胎週数別新版K式発達検査領域別発達指数（DQ）評価の割合

姿勢・運動

認知・適応

言語・社会

85〜
70〜84
〜69

在胎週数

表1　海外ネットワーク研究との在胎25週未満児の発達予後の比較

	NRN-Japan	EPICure 1[5]	NRN-Japan	NICHD[6]
Year of birth	2003-2005	1995	2003-2005	2002-2004
Admitted to NICU, n	1,057	808	652	1,395
GA（weeks）	22-25	22-25	22-24	22-24
Mortality（% in admission）	275（26%）	500（62%）	215（33%）	957（69%）
Follow-up	n＝562	n＝283	n＝322	n＝405
age（median or mean）	36m	30m	36m	20m
% of survivors	72%	92%	74%	·92%
Evaluation	KSPD	Bayley Ⅱ	KSPD	Bayley Ⅱ
% of follow-up infants	n＝331（59%）	n＝251（89%）	n＝186（58%）	n＝384（95%）
DQ＜70 or MDI＜70 % in measurement	32%		36%	45%
DQ＜70 or PDI/MDI＜70 % in follow-up	31%（主治医判定含む）	30%（主治医判定含む）	36%（主治医判定含む）	41%（主治医判定含まず）

KSPD：新版K式発達検査

ータの集積が可能となり，施設毎では例数の少ない在胎22，23週や出生体重500g未満の児の発達予後も明らかになってきた[3]．図2で示したように在胎22週，23週では，評価例の約35%が発達遅滞，約30%が境界発達であり，正常発達の評価は各々27%，27%であること，24週，25週であってもその割合は29%，36%にすぎないことなどから，超早産児の発達予後は今後の周産期医療の質の改善の重要課題である．

また，発達予後と出生前因子，母体・新生児の合併症や治療との関連の解析結果も報告されている[4]．死亡またはDQ＜70と有意な関連がみられた要因は，壊死性腸炎を含む消化管穿孔，脳室周囲白質軟化症，敗血症，修正36週時の慢性肺疾患であった．主治医判定による発達遅滞を含めると，上記の要因に加えて，3度以上の脳室内出血，未熟児網膜症の治療が挙げられた．極低出生体重児の発達予後のアウトカムと関連を認めた要因の治療や介入の検討は，周産期医療の向上に寄与する重要なプロダクトである．

現行の発達評価法の問題点

1）K式未実施例，主治医判定例の評価

K式未実施例は実施例にくらべ，在胎期間や出生体重に差はないが，新生児合併症の中で，3度以上のIVH，脳室周囲白質軟化症，修正36週時の慢性肺疾患の割合が高く，予後では脳性麻痺，失明の合併の割合が高かった．神経学的障害の合併のため，発達検査が実施できない例や，明らかな発達遅滞例では発達検査が実施されなかったと考えられる．失明や運動機能障害などで発達検査が実施できない例での評価法のプロトコール化が必要である．

2）海外の予後データとの比較と発達予後の海外へ発信

K式は日本のみで行われる検査であり，海外からの報告との発達予後の比較が難しい．表1に，海外の新生児

ネットワーク研究での在胎25週未満児の発達予後との比較を示した[5][6]．海外ではBayley検査が発達評価に用いられることが多く，Bayley IIでは，mental development index（MDI）またはpsychomotor development index（PDI）が70未満を発達遅滞と評価している．検査法は異なるが発達遅滞の割合はNRNのK式DQが70未満の割合と同等であった．日本の新生児医療のアウトカムとして発達予後を海外に発信するためには，より高いフォローアップ率，発達検査実施率が求められると同時に，グローバルスタンダードな発達検査法を用いることは今後の課題である．

3) 一般児との発達評価の比較

　極低出生体重児の3歳時のK式DQの分布は，正規分布とくらべ低得点に分布する例が多く，一般児を対象としたK式標準化時におけるDQの標準偏差値より大きくなっていた．NRNではDQ70未満を発達遅滞と評価しているが，厳密に「遅滞」と評価するには，一般児も同一の検査法で同時期に評価して比較することが必要とされる[7]．

4) 発達障害の評価

　低出生体重児は，自閉性障害スペクトラム，注意欠陥多動性障害，発達性協調運動障害，学習障害のリスク要因と考えられているが，フォローアップにおいてのそれぞれの評価方法は確立されていない．実際の合併率も，評価法が統一でないこともあり報告によって異なる[8]．これらの評価方法および評価後の支援の確立もハイリスク児のフォローアップの重要な課題である．

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Outcomes of Infants Born at 22 and 23 Weeks' Gestation

WHAT'S KNOWN ON THIS SUBJECT: The remarkable improvement in the survival of extremely premature infants has been well documented. However, there have been few cohort studies large enough to determine the neurodevelopmental outcomes of survivors born at 22 or 23 weeks.

WHAT THIS STUDY ADDS: The proportions of unimpaired or minimally impaired were 12.0% at 22 weeks (n = 75) and 20.0% at 23 weeks (n = 245). The outcomes were inferior compared with those for infants born at 24 and 25 weeks, but were improved compared with those in previous studies.

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abstract

OBJECTIVE: To provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age.

METHODS: The study cohort consisted of 1057 infants born at 22 to 25 weeks in the Neonatal Research Network, Japan. Neurodevelopmental impairment (NDI) at 36 to 42 months' chronological age was defined as any of the following: cerebral palsy, hearing impairment, visual impairment, and a developmental quotient <70. A systematic review was performed by using databases of publications of cohort studies with neonatal and neurodevelopmental outcomes at 22 and 23 weeks.

RESULTS: Numbers and incidences (%) of infants with death or NDI were 60 (80%) at 22 weeks and 156 (64%) at 23 weeks. In logistic regression analysis, gestational ages of 22 weeks (odds ratio [OR]: 5.40; 95% confidence interval [CI]: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) were associated with increased risk of death or NDI compared with 24 weeks, but a gestational age of 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) was associated with decreased risk of death or NDI. In the systematic review, the medians (range) of the incidence of death or NDI in 8 cohorts were 99% (90%–100%) at 22 weeks and 98% (67%–100%) at 23 weeks.

CONCLUSIONS: Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants at born at 24 weeks. However, outcomes were improved compared with those in previous studies. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation. *Pediatrics* 2013;132:62–71

The remarkable improvement in the survival of extremely low birth weight infants has been well documented.[1,2] Increased extremely low birth weight infant survival rates have paralleled improvements in prenatal and neonatal care.[3] The outcomes after 24 weeks' gestational age have been well estimated and evaluated.[4–21]

There recently have been several notable reports on 22 and 23 weeks' gestational age; the short-term outcomes of these extremely premature infants seem to have improved, but the long-term outcomes are still unfavorable.[6–18] Decisions to initiate or withhold intensive care for these extremely premature infants are highly controversial, in contrast to those for infants born at 24 and 25 weeks' gestational age.[22–24] Physicians and parents contemplating the prognosis of extremely preterm infants require reliable information based on gestational age with which to plan care around the time of birth and thereafter.[4,25]

The aim of this study was to provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age and to compare them with those of infants born at 24 or 25 weeks from a large multicenter cohort and a systematic review.

METHODS

Study Subjects and Definitions

A total of 48 tertiary centers participated in a multicenter follow-up study of the Neonatal Research Network, Japan, in infants born at 22 to 25 weeks between January 1, 2003, and December 31, 2005.[5,6,26,27] Each center registered all very low birth weight infants who were admitted to the NICU within 28 days after birth, including infants transferred to the centers after birth (outborn). The infants who were born alive but died in the delivery room in the centers were registered. Infants

who were recognized as born before 22 weeks 0 day were excluded.[6]

Demographic, perinatal, and infant data were collected from each center by using previously described definitions.[5,6,26,27] Gestational age was determined in the following order: obstetric history based on last menstrual period, with confirmation or correction by obstetric examination by using ultrasonography at the health checkup for pregnant women during the first trimester, and postnatal physical examinations of neonates. Premature rupture of membranes was defined as rupture of membranes before the onset of labor. Antenatal steroid use was defined as administration of any corticosteroid to accelerate fetal lung maturity. Maternal transport meant only emergency transport. Respiratory distress syndrome was diagnosed by using clinical and radiographic findings. Chronic lung disease (CLD) was defined as the use of supplemental oxygen on the 28th day after birth, and 36-week CLD was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks. Symptomatic patent ductus arteriosus was diagnosed on the basis of both echocardiographic findings and clinical evidence of volume overload because of left-to-right shunt. Intraventricular hemorrhage (IVH) was reported according to the classification of Papile et al.[28] Cystic periventricular leukomalacia was diagnosed by cranial ultrasound or head MRI scans. Sepsis was defined as culture-proven septicemia or bacteremia at any time during the NICU stay. Necrotizing enterocolitis was defined according to the classification of Bell et al[29] as stage II or higher. The treatment of retinopathy of prematurity (ROP) was laser coagulation, cryocoagulation therapy, or both.

Neurodevelopmental Assessments

A comprehensive neurodevelopmental assessment was performed on the surviving infants at 36 to 42 months'

chronological age. The assessment consisted of neurologic assessment, functional classification of hearing and visual ability, developmental evaluation, growth assessment, medical and social history, and interviews at each participating center.

The neuromotor examinations were performed by a trained pediatrician, not necessarily blinded to the perinatal details. Cerebral palsy (CP) was defined as a nonprogressive, nontransient central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture.[30] Profound CP was defined as a Gross Motor Function Classification System (GMFCS) level of 4 or 5.[31] Children with an unknown CP level were classified as having profound impairment. Children with any type of CP who were defined as GMFCS level 1 were excluded from the CP group and were included in the minimally impaired group.[13] Hearing impairment was defined as when amplification was required. Visual impairment was defined as blindness with no functional vision in 1 or both eyes.

The assessment of cognitive function was performed by using the Kyoto Scale of Psychological Development (KSPD) test.[32] This test was administered by experienced testers who were certified psychologists blinded to the perinatal details at each center. The developmental quotient (DQ) was derived by dividing developmental age by chronological age. A DQ score of 100.6 ± 13.4 represents the mean $\pm$ 1 SD at the time of standarization.[32] A DQ score <70 was interpreted as representing significantly delayed performance. If the KSPD assessment was not available, the pediatrician estimated the child's development level as delayed or not delayed. In cases judged as delayed, the developmental level was assumed as equivalent to a DQ score <50 in this study.

Neurodevelopmental impairment (NDI) was defined as any of the following: CP with a GMFCS level 2 to 5, hearing impairment, visual impairment, or a DQ score <70. Profound NDI was defined as profound CP and/or a DQ score <50.

Statistical Analyses

Characteristics by gestational age are described as means and SDs for continuous variables and as numbers and proportions for binary and categorical variables. Logistic regression was used to evaluate the relationship between risk factors and death or NDI at 3 years of age. We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) by logistic regression using a reference of infants born at 24 weeks' gestational age. The selected biological and perinatal characteristics were gender, multiple birth, premature rupture of membranes, antenatal steroid use, maternal transport, being outborn, use of cesarean delivery, and gestational age because these were identified as variables associated with outcomes in previous follow-up studies.[7,33–38]

Systematic Review of Studies With Neonatal Outcomes at 22 and 23 Weeks' Gestation

The PubMed and Cochrane Library databases were searched by using a combination of the following words: extremely premature, infant, neurodevelopment, and outcome. The language was restricted to English. All potentially relevant titles and abstracts were retrieved and assessed for eligibility. The reference lists of relevant articles were reviewed, and relevant citations were retrieved if they had not been obtained in the primary search. Publications were selected for inclusion if they contained the following: (1) a publication date between January 1, 2000, and June 30, 2012; (2) outcomes of infants born during or after 1990; (3) the numbers of cases of death and NDI

at 18 to 42 months for infants born at <28 weeks' gestational age; and (4) the numbers of evaluated infants at 18 to 42 months. For each eligible study, all reported components of death, NDI, and follow-up rates were extracted. The latest reports were chosen from the same cohorts or the same area.
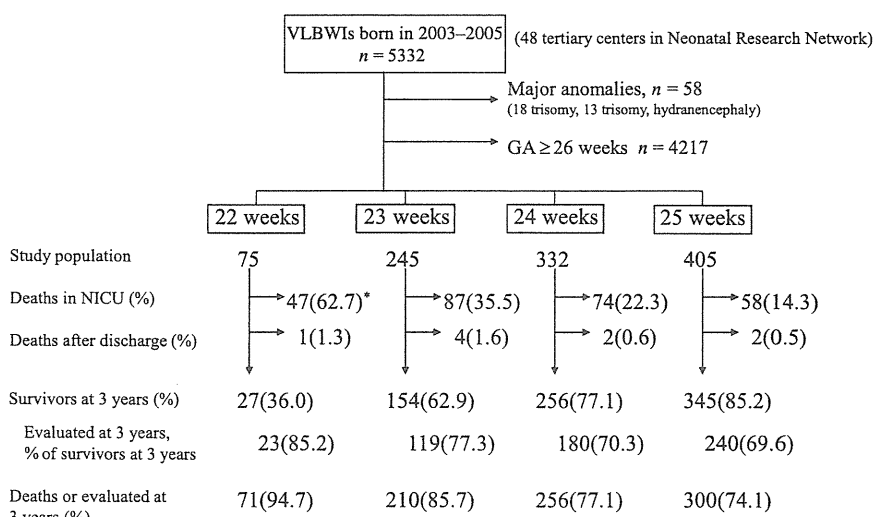
RESULTS

During the study period, 1057 infants born at <26 weeks were registered with the Neonatal Research Network (Fig 1). Of these, 266 died in the NICU (25.2%), including 1 case not admitted to the NICU, and 791 (74.8%) survived to discharge. Nine infants died after discharge. Between January 2006 and December 2008, 562 of the 782 survivors visited a site for standardized follow-up assessment.

Demographic and perinatal characteristics, neonatal morbidities, and interventions were not different between infants evaluated and not evaluated, except that evaluated infants were more likely to require treatment of ROP (234 [41.7%] of evaluated infants, 73 [33.2%] of infants who were not evaluated), and were less likely to be outborn (47 [8.9%] of evaluated infants, 29 [13.2%] of infants

who were not evaluated), experience neonatal seizure (30 [5.3%] of evaluated infants, 25 [11.4%] of infants who were not evaluated), and have grade 3–4 IVH (48 [8.6%] of evaluated infants, 30 [13.6%] of infants who were not evaluated).

As shown in Table 1, stratifying demographic and perinatal characteristics according to gestational weeks, infants with a birth weight <400 g were particularly common at 22 weeks. The use of antenatal steroids, maternal transport, being outborn, and cesarean delivery increased with increasing gestational weeks. Among neonatal morbidities, proportions of respiratory distress syndrome, neonatal seizure, IVH grades 3–4, and sepsis tended to decrease with increasing gestational weeks. Proportions of CLD at 36 weeks' corrected gestational age, ligation for patent ductus arteriosus, cystic periventricular leukomalacia, necrotizing enterocolitis, and ROP requiring any treatment were low in infants born at 22 weeks.

Table 2 shows neurodevelopmental outcomes grouped by gestational weeks of the evaluated infants. Seventy-five (13.7%) infants had CP,

	VLBWIs born in 2003–2005 n = 5332	(48 tertiary centers in Neonatal Research Network)

Major anomalies, n = 58 (18 trisomy, 13 trisomy, hydranencephaly)

GA ≥26 weeks n = 4217

	22 weeks	23 weeks	24 weeks	25 weeks
Study population	75	245	332	405
Deaths in NICU (%)	47(62.7)*	87(35.5)	74(22.3)	58(14.3)
Deaths after discharge (%)	1(1.3)	4(1.6)	2(0.6)	2(0.5)
Survivors at 3 years (%)	27(36.0)	154(62.9)	256(77.1)	345(85.2)
Evaluated at 3 years, % of survivors at 3 years	23(85.2)	119(77.3)	180(70.3)	240(69.6)
Deaths or evaluated at 3 years (%)	71(94.7)	210(85.7)	256(77.1)	300(74.1)

FIGURE 1
Study subjects by gestational age groups. *Includes 1 case born alive but not admitted to the NICU. GA, gestational age; VLBWI, very low birth weight infants.

TABLE 1 Characteristics of Study Cohort

	Gestational Age				Total N =1057
	22 Weeks (n = 75)	23 Weeks (n = 245)	24 Weeks (n = 332)	25 Weeks (n = 405)	
Demographic and perinatal characteristics					
BW, mean ± SD, g	488 ± 72	575 ± 80	634 ± 103	741 ± 137	651 ± 137
BW <400 g, n/N (%)	7/75 (9.3)	3/245(1.2)	7/332(2.1)	9/405(2.2)	26/1057 (2.5)
Male, n/N (%)	32/75 (42.7)	133/244[a] (54.5)	163/332 (49.1)	219/403[a] (54.3)	547/1054[a] (51.9)
Multiple birth, n/N (%)	16/75 (21.3)	60/245 (24.5)	61/332 (18.4)	82/405 (20.2)	219/1057 (20.7)
Preterm rupture of membranes, n/N (%)	36/75 (48.0)	96/245 (39.2)	140/332 (42.2)	148/405 (36.5)	420/1057 (39.7)
Antenatal steroid use, n/N (%)	16/75 (21.3)	79/245 (32.2)	137/332 (41.3)	177/405 (43.7)	409/1057 (38.7)
Maternal transport, n/N (%)	38/75 (50.7)	151/245 (61.6)	207/331[a] (62.5)	247/402[a] (61.4)	643/1053[a] (61.1)
Outborn, n/N (%)	6/75 (8.0)	20/245 (8.2)	31/332 (9.3)	41/405 (10.1)	98/1057 (9.3)
Cesarean delivery, n/N (%)	18/75 (24.0)	104/245 (42.4)	218/332 (65.7)	297/405 (73.3)	637/1057 (60.3)
In-hospital morbidities and interventions, n/N (%)					
RDS diagnosed	60/74[a] (81.1)	191/245 (78.0)	251/332 (75.6)	309/405 (76.3)	811/1056[a] (76.8)
CLD at 36 weeks[b]	15/71[a] (21.1)	71/236[a] (30.1)	121/319[a] (37.9)	133/392[a] (33.9)	340/1018[a] (33.4)
PDA ligation	4/72[a] (5.6)	34/238[a] (14.3)	50/316[a] (15.8)	41/389[a] (10.5)	129/1015[a] (12.7)
Neonatal seizure	11/74[a] (14.9)	28/245 (11.4)	40/331[a] (12.1)	30/405 (7.4)	109/1055[a] (10.3)
IVH grade 3–4	18/74[a] (24.3)	52/241[a] (21.6)	48/328[a] (14.6)	49/403[a] (12.2)	167/1046[a] (16.0)
Cystic PVL	2/74[a] (2.7)	10/244[a] (4.1)	13/331[a] (3.9)	22/405 (5.4)	47/1054[a] (4.5)
Sepsis	17/74[a] (23.0)	58/244[a] (23.8)	73/331[a] (22.1)	59/405 (14.6)	207/1054[a] (19.6)
Necrotizing enterocolitis	1/74[a] (1.4)	16/245 (6.5)	10/331[a] (3.0)	15/405 (3.7)	42/1055[a] (4.0)
ROP requiring treatment	15/75[a] (20.0)	73/245 (29.8)	102/331[a] (30.8)	128/405 (31.6)	318/1056[a] (30.1)

BW, birth weight; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.
[a] There were cases without data on this characteristic.
[b] CLD at 36 weeks was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks.

TABLE 2 Neurodevelopmental Outcomes at 3 Years of Age According to Gestational Age

	Gestational Age				Total
	22 Weeks	23 Weeks	24 Weeks	25 Weeks	
Evaluated at 3 years, n	23	119	180	240	562
CP, n/N (%)[a]	5/23 (21.7)	21/118[b] (17.8)	14/173[b] (8.1)	35/234[b] (15.0)	75/548 (13.7)
Profound CP	4/23 (17.4)	12/118[b] (10.2)	9/173[b] (5.2)	20/234[b] (8.5)	45/548 (8.2)
Hearing impairment, n/N (%)[a]	0/23 (0.0)	4/119 (3.4)	2/168[b] (1.2)	3/234[b] (1.3)	9/544 (1.7)
Visual impairment, n/N (%)[a]	2/23 (8.7)	12/118[b] (10.2)	6/175[b] (3.4)	5/231[b] (2.2)	25/547 (4.6)
Cognitive delay, n/N (%)[a]	12/21[b] (57.1)	55/110[b] (50.0)	49/152[b] (32.2)	58/208[b] (27.9)	174/491 (35.4)
KSPD DQ of 50–69	5/11 (45.5)	12/58 (20.7)	27/104 (26.0)	31/145 (21.4)	75/318 (23.6)
KSPD DQ of <50	0/11 (0.0)	7/58 (12.1)	11/104 (10.6)	17/145 (11.7)	35/318 (11.0)
Judgment of delay by pediatrician	7/10 (70.0)	36/52 (69.2)	11/48 (22.9)	10/63 (15.9)	64/173 (37.0)
NDI, n/N (%)[a]	12/23 (52.2)	65/114[b] (57.0)	53/142[b] (37.3)	78/212[b] (36.8)	208/491 (42.4)
Profound NDI	7/23 (30.4)	45/114[b] (39.5)	23/142[b] (16.2)	36/212[b] (17.0)	111/491 (22.6)
Death or NDI, n/N (%)[c]	60/75 (80.0)	156/245 (63.7)	129/332 (38.9)	138/405 (34.1)	483/1057 (45.7)
Death or Profound NDI	55/75 (73.3)	136/245 (55.5)	99/332 (29.8)	96/405 (23.7)	386/1057 (36.5)
Unimpaired/minimally impaired, n/N (%)[c]	9/75 (12.0)	49/245 (20.0)	89/332 (26.8)	134/405 (33.1)	281/1057 (26.6)

Profound CP was defined as a GMFCS level of 4 or 5. Children who were defined as GMFCS level 1 were excluded and were included in the minimally impaired group. Hearing impairment was defined as requiring amplification. Visual impairment was defined as blind with no functional vision in 1 or both eyes. Cognitive delay was defined as a DQ score <70; if the child was unable to complete the KSPD assessment, the pediatrician estimated the child's developmental level as delayed or not. In cases judged as delayed, the developmental level was assumed to be equivalent to a KSPD DQ of <50. NDI was defined as any of the following: CP with a GMFCS level of 2 to 5, hearing impairment, visual impairment, or DQ score <70. Profound NDI was defined as profound CP and/or a DQ score of <50. Children with an unknown CP level were classified into profound impairment.
[a] (%): percentage of infants with data of the assessment.
[b] There were cases without the assessment.
[c] (%): percentage of the study population.

including 45 (8.2%) with profound CP. Profound CP was more often found in infants born at 22 weeks than in those born at the other weeks. There was no obvious association between hearing impairment and increasing gestational weeks. The proportions with visual impairment were equally high at 22 and 23 weeks. Cognitive delay was found in 174 (35.4%) of the 491 evaluated infants, 75 (15.3%) with a DQ between 50 and 69, and 99 (20.2%) with a DQ ≤50. Of the 318 infants assessed by the KSPD, 20 (6.3%) had a DQ <50 and 75 (23.6%) had a DQ of 50 to 70. In infants with 22 and 23 weeks' gestational age, those whose cognitive function was assessed by pediatricians were more likely to

have blindness (19%) or CP (37%) than infants assessed by the KSPD (3% for blindness and 9% for CP). A total of 208 (42.4%) fully evaluated infants had NDI, with 111 (22.6%) having profound NDI. The incidences of both death or NDI and death or profound NDI were clearly related to gestational weeks. Overall, 281 (26.6%) of the 1057 subjects were unimpaired or minimally impaired at 3 years of age: 9 (12.0%) of whom were born at 22 weeks' gestational age, 49 (20.0%) of whom were born at 23 weeks' gestational age, 89 (26.8%) of whom were born at 24 weeks' gestational age, and 134 (33.1%) of whom were born at 25 weeks' gestational age.

In logistic regression after adjusting for biological and perinatal variables, being born at 22 weeks (OR: 5.40; 95% CI: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) in comparison with the reference (24 weeks) increased the risk of death or NDI, but being born at 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) decreased the risk of death or NDI. When infants with birth weights <400 g were excluded from the model to eliminate the effect of severe growth restriction, a gestational age of 22 weeks (OR: 5.77; 95% CI: 2.55–13.04) and 23 weeks (OR: 2.22; 95% CI: 1.43–3.44) compared with a gestational age of 24 weeks similarly increased the risk of death or NDI.

From the systematic review, 46 publications reporting outcomes and follow-up rates were identified, 30 of which described outcomes at 18 to 42 months; however, only 12 included the numbers of cases of death and NDI at 18 to 42 months for a total of 15 different cohorts. Eight of these 15 cohorts contained data that met the definition of NDI in this study. The numbers of cases of death, NDI, and evaluated infants were reported for a total of 9717 extremely premature infants at 18 to 42 months for all 8 publications.[7-18] Year,

country of birth, and type of study cohort are summarized in Table 3 and 4 by gestational weeks. Mortality rates ranged from 64% to 100% in infants born at 22 weeks' gestation, from 37% to 100% at 23 weeks' gestation, and from 19% to 65% at 24 to 27 weeks' gestation. Follow-up rates ranged from 0% to 100% for 22 and 23 weeks' gestation and from 70% to 99% for 24 to 27 weeks' gestation (Table 3). The incidence of death or NDI ranged from 80% to 100% for 22 weeks' gestational age, from 64% to 100% for 23 weeks' gestational age, and from 36% to 82% for 24 to 27 weeks' gestational age (Table 4).

DISCUSSION

In a large cohort of extremely preterm infants born at <26 weeks' gestational age, we found that 50% to 60% of survivors born at 22 and 23 weeks' gestational age and ~30% of survivors at 24 and 25 weeks' gestational age had disability at 3 years of age in terms of mental and psychomotor development. On the other hand, nearly half of the infants born even at 22 or 23 weeks, and who had survived to 3 years of age, were unimpaired or minimally impaired, although these proportions were lower than those for infants born at 24 or 25 weeks. The incidence of death or NDI was clearly related to gestational weeks, consistent with many previous studies.[3,5-21] Among the survivors, however, the incidence of NDI for those born at 22 weeks was nearly equal to that for those born at 23 weeks. This result was probably affected by the high mortality for 22 weeks, meaning that the most severe cases born at 22 weeks died early in life. In addition, the proportion of NDI at 22 weeks should be interpreted with caution because the number of survivors in this category was low.

The strengths of our study include the relatively large population with a lower

mortality rate of infants born at 22 and 23 weeks than in previous studies, as shown in Table 3. As a result, more infants survived and could be evaluated at 3 years of age.

In the evaluated infants, the proportions of CP, hearing impairment, visual impairment, and a DQ <70 were similar to those in previous studies.[7,11,15,19] The incidence of profound CP was slightly higher than in a report from the NICHD, especially at 22 and 23 weeks.[7] One reason for this was that we classified the infants with an unknown CP level as having profound impairment. We decided to choose the strictest judgment for NDI because the judgment might have a major impact on the conclusion of the study. If the infants with an unknown CP level were excluded from the profound impairment group, the incidence of profound CP decreased to 2 (8.7%) for those born at 22 weeks and to 10 (8.5%) for those born at 23 weeks, which is equal to the incidence in the NICHD data.[7]

The proportion of infants with a DQ <70 was higher than the proportions with other impairments. Approximately half of the infants born at 22 and 23 weeks' gestation were found to have cognitive delay, but the corresponding proportion was one-third at 24 and 25 weeks' gestation. Infants at 22 and 23 weeks were more likely to be judged by a pediatrician and they more often had other handicaps such as blindness or CP. These impairments might prevent completion of the KSPD test.[13] Because pediatricians were not always blinded to perinatal and neonatal morbidities and interventions, judgment by a pediatrician without a test could result in overestimation of the proportion of cognitive delay in infants at 22 and 23 weeks' gestational age. A higher incidence of impaired cognitive development in infants born at very low gestational ages has been described in several reports.[7,11,13,15-21,25] Although

TABLE 3 Survival and Neurodevelopmental Outcomes of Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	309/322 (96)	—	—	342/441 (78)	22–23 weeks; 104/112 (93)	22–23 weeks; 750/763 (98)	24 weeks; 294/632 (47)	22–24 weeks; 405/450 (90)	24 weeks; 489/632 (77)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks; 504/528 (96)	<23 weeks; 15/21 (71)	<23 weeks; 515/528 (98)	567/916 (62)	214/298 (72)	679/916 (74)	24–25 weeks; 906/3033 (30)	24–25 weeks; 1229/1702 (72)	24–25 weeks; 1401/3033 (46)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	32/33 (97)	—	—	28/35 (80)	—	—	22–27 weeks; 56/220 (25)	22–27 weeks; 163/172 (95)	22–27 weeks; 196/288 (68)
EPIBEL (11,12) (Belgium, 30–42 mo, 1999–2000, population-based)	28/28 (100)	0/0 (0)	28/28 (100)	40/41 (98)	1/1 (100)	40/41 (98)	24–26 weeks; 91/182 (50)	24–26 weeks; 88/91 (97)	24–26 weeks; 142/182 (78)
EPICure (13,14) (UK, 30 mo median, 1995, population-based)	136/138 (99)	2/2 (100)	137/138 (99)	216/241 (90)	25/25 (100)	230/241 (95)	24–25 weeks; 525/806 (65)	24–25 weeks; 279/281 (99)	24–25 weeks; 661/806 (82)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	16/16 (100)	0/0 (0)	16/16 (100)	30/30 (100)	0/0 (0)	30/30 (100)	24–27 weeks; 224/549 (41)	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	8/10 (80)	2/2 (100)	9/10 (90)	12/18 (67)	5/6 (83)	12/18 (67)	24–25 weeks; 16/55 (29)	34/39 (87)	22/55 (40)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	<24 weeks; 37/37 (100)	<24 weeks; 0/0 (0)	<24 weeks; 37/37 (100)	24–27 weeks; 154/349 (44)	24–27 weeks; 183/195 (94)	24–27 weeks; 206/349 (59)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	48/75 (64), 43/69 (62)[b]	23/27 (85)	60/75 (80)	91/245 (37), 82/225 (36)[b]	119/154 (77)	156/245 (64)	24–25 weeks; 139/737 (19), 127/605 (19)[b]	24–25 weeks; 420/601 (70)	24–25 weeks; 267/737 (36)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; VON, Vermont Oxford Network; —, data was not shown.

a Mortality included cases who died in the delivery room, died in the NICU, or died after discharge until evaluation, but not cases who died intrapartum.
b Mortality excluding the infants transferred after birth to the participating centers from cases in footnote a.

the reason is unclear, various factors affect cognitive development, such as socioeconomic, environmental, and nutritional factors.[8,19,20,34,37] It could be assumed that extreme prematurity of the brain itself is critical for later brain functions.[39–41] Cognitive delay judged by pediatricians may have overestimated the number of infants with a DQ <50.

The most important result in this study was the proportion of unimpaired/ minimally impaired infants: 9 (12.0%) of those born at 22 weeks and 49 (20.0%) of those born at 23 weeks. The risks of death or NDI were 5 times higher at 22 weeks' gestational age and 2 times higher at 23 weeks' gestational age than in those born at 24 weeks in a logistic regression model. Resuscitation or intensive care of infants born at 22 or 23 weeks is a very controversial issue.[2,4,7,10,12,20] There is widespread consensus that the aim of neonatal resuscitation should be the qualitatively acceptable survival of the child. However, the guidelines for resuscitation of these infants have not been unified across countries or institutions.[4,22–25,42,43] There could be differences in medical behavior and attitudes associated with the different cultural, social, and legal backgrounds of each country; this could affect the survival and morbidity data of infants born at the threshold of viability. Comparing death or NDI with that in other cohorts, the mortality rate in this study was lower, especially at 22 and 23 weeks, although eligibility and exclusion criteria and the follow-up rate of the study cohorts were not all the same. The incidence of death or NDI was also low, meaning that the proportion of survivors with NDI at 3 years of age was not higher. The follow-up rate, however, may have affected the proportion of NDI, the same as in studies of Mercier et al[8] and Kutz et al.[17] We chose the strictest criteria

TABLE 4 CP and Cognitive Delay of the Evaluated Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	CP, n/Evaluated Infants (%)	Cognitive Delay, n/Evaluated Infants (%)	NDI, n/Evaluated Infants (%)	CP, n/Evaluated Infants (%)	Cognitive Delay, n/Evaluated Infants (%)	NDI, n/Evaluated Infants (%)	CP, n/Evaluated Infants (%)	Cognitive Delay, n/Evaluated Infants (%)	NDI, n/Evaluated Infants (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	—	—	—	22–23 weeks; 28/105 (27)	22–23 weeks; MDI <70: 63/102 (62); PDI <70: 46/104 (44)	22–23 weeks; 72/103 (70)	24 weeks; 57/298 (19)	24 weeks; MDI <70: 133/282 (47); PDI <70: 88/280 (31)	24 weeks; 155/284 (55)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks CP and/or cognitive delay; 11/15(73)	—	<23-weeks; 11/15 (13)	CP and/or cognitive delay; 112/214 (52)	—	112/214 (52)	24–25 weeks CP and/or cognitive delay; 495/1499 (33)	—	24–25 weeks; 495/1229 (40)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	—	—	—	—	—	—	22–27 weeks; 16/163 (10)	22–27 weeks; 26/163 (16)	24–27 weeks; 80/163 (49)
EPIBEL (11,12) (Belgium, 30–42 mo, 1999–2000, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	0/1 (0)	0/1 (0)	0/1 (0)	24–26 weeks; 19/77 (25)	24–26 weeks; MDI <70: 22/77 (29); PDI <70: 37/77 (48)	24–26 weeks; 51/88 (58)
EPICure 1 (13,14) (UK, 30 mo median, 1995, population-based)	—	—	1/2 (50)	—	22–23 weeks; 7/26 (27)	14/25 (56)	22–25 weeks; 50/306 (16)	24–25 weeks; 78/257 (30)	24–25 weeks; 136/279 (49)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	—	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	—	—	1/2 (50)	—	—	0/5 (0)	—	—	24–25 weeks; 6/34 (18)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	(All cases dead)	(All cases dead)	(All cases dead)	24–27 weeks; 5/53 (9)	24–27 weeks; 9/53 (17)	24–27 weeks; 52/183 (28)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	5/23 (22)	12/21 (57)	12/23 (52)	21/118 (18)	55/110 (50)	65/114 (57)	24–25 weeks; 49/407 (12)	24–25 weeks; 107/360 (30)	24–25 weeks; 131/354 (37)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; MDI, mental developmental index; PDI, psychomotor developmental index; VON, Vermont Oxford Network; —, data was not shown.

for NDI, meaning that impairments having CP or cognitive delay without assessment of degrees were considered as profound impairments. When discussing intervention and treatment of infants at the threshold of viability, we should not do opportunistic assessment because severe impairments would have a major impact on the surviving infants and their parents for life. This strictest criteria for NDI could provide overestimated impairments and the possible-worst outcome. Although there is no definite consensus regarding what probability of survival without profound impairment justifies intensive care,[44] the results of this study provide important information to consider in current treatment.

There are several limitations to this study. The first concerns the follow-up rate, which was ~70% in infants born at 24 and 25 weeks' gestation. It is unclear how the follow-up rate affects the true incidence of severe disability.[45,46] Several reports on attrition in follow-up programs suggest that infants with serious developmental delays or disabilities are more likely to drop out of follow-up.[47–49] Coincident with this, the nonevaluated group had a higher percentage of IVH grade 3–4 than did the evaluated group. This could be relevant and confer a higher risk of NDI in the infants.

The second limitation is a lack of registration of stillbirth and clear classifications of withdrawing/withholding intensive care in the delivery room, which are important when we compare the survival rate with those in other cohort studies.[21] The network defines stillbirth as an infant who does not show any cardiac pulse under vigorous resuscitation after 22 weeks of gestational age regardless of birth weight, although the number of stillbirths was not collected, which remained almost constant at <1% of the total number of infants registered each year.[6] The

numbers of stillbirths or deaths in the delivery room in hospitals other than the participating centers were also not collected. The mortality rate, however, did not change after excluding the outborn infants in this study, as shown in Table 3.

The last limitation concerns the use of the KSPD test for cognitive evaluation. Although the KSPD test is written only in Japanese, it is a validated and standardized developmental test battery available for all centers participating in the follow-up study in Japan.[32] KSPD assessment is not comparable to, for instance, the Bayley Scales of Infant Development III, which is widely used for cognitive evaluation at this age.[50] Additionally, we could not collect socioeconomic information, which is known to be associated with infants' future developmental state.[51] The quality of life of the infants, their later neurologic outcomes, and academic and social achievements into adulthood should also be elucidated in future studies.

CONCLUSIONS

Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants born at 24 and 25 weeks' gestation, but outcomes were improved compared with those in previous studies from a systematic review. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation.

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A GLANCE INTO THE FUTURE: FECAL TRANSPLANTS FOR WEIGHT LOSS: Each day I am bombarded with information about how to lose weight. There seems to be an almost endless array of diet or exercise recommendations and oodles of gadgets "guaranteed" to work. In the past few months, one of my relatives has tried to lose weight following the South Beach diet, then a Paleolithic diet, and most recently using a smart phone application. Maybe she should try a fecal transplant. As reported in The New York Times (Health: March 28, 2013), the bacterial flora in our guts may be at least partially responsible for weight loss or gain. Researchers have never quite understood all the reasons why people lose weight following gastric bypass surgery. However, in a recent study conducted in mice, researchers concluded that approximately 20% of the weight loss is most likely due to a change in bacterial flora. Fattened mice that underwent gastric bypass surgery lost weight and had altered intestinal flora. Mice that underwent a sham surgery where the intestine was simply severed and re-anastomosed did not lose weight and the microbiota did not change. Next, intestinal contents from each group were transplanted into mice lacking intestinal flora. The mice that received material from the bypass surgery group lost weight while the mice receiving material from the sham group did not. In a study conducted in adults with potential gastrointestinal disorders, researchers found that indirect evidence of the presence of Methanobrevibacter smithii *in the gut was directly related to body mass. The individuals with the highest levels of methane and hydrogen on breath tests were more likely to have more body fat. One possible explanation for this finding is that* M. smithii *may contribute to the breakdown of foodstuffs, making more calories available. The general dieter may not be ready for a fecal transplant to help increase weight loss, but the more we learn about our gut and the bacteria that inhabit it, the more we realize how intertwined we are.*

Noted by WVR, MD

長期フォローアップと多種職連携

河野 由美

はじめに

近年の周産期・新生児医療の進歩により，超早産児や超低出生体重児の生命予後の向上のみならず，先天異常をもつ新生児の治療成績や生命予後も著しく改善した。しかしながら，染色体異常や複雑な先天異常を合併した児の退院後の健康状態や成長・発達については不明なことも多く，周産期医療に携わる医療従事者の知識も十分ではない。

先天異常合併患者の成人期までの健康状態に関する調査によると，幼年期には死亡や疾病合併率が高く，年齢とともに健康状態は改善するが，成人に達しても疾患に関連した症候を合併している例は少なくない[1]。Down 症候群では，合併する先天性心疾患により生命予後は異なり，心疾患がなければ約 90%の児が 10 年以上生存することが知られ[2]，関連する合併症や自然経過を理解した上で，長期にわたって年齢に応じた検査，診断，健康管理，指導や支援が必要とされる。眼科，耳鼻科，整形外科などの各診療科や，療育施設，学校などとの連携をとって長期的かつ包括的にフォローアップする医師が必要であり，多くの場合小児科医がその責務を担う。児の成長・発達を含めたトータルなケアが長期的に必要なことは，超低出生体重児のフォローアップと同様である[3]。本稿では，染色体異常や先天異常症候群の長期フォローアップにおける小児科医の役割，フォローアップに必要な疾患への理解，患児や家族が必要とする支援，多種職との連携について総論を述べる。

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フォローアップにおける小児科医の役割

染色体異常や先天異常症候群の児のフォローアップは，実際のところ医学的に煩雑であり，困難な事柄にぶつかることが多い。慢性疾患の治療の責任以外にも，先天異常がもたらす遺伝的，心理・社会的な意味での責任もある。Stein[4]によれば，慢性疾患児の長期管理方法に小児科医は以下の三つのいずれかの方法をとることができる。①全管理を特殊専門医または総合治療チームに任せる，②小児科医自身がすべての管理を引き受ける，③小児科医が，特殊専門医あるいはチームと共同で管理を行う，のいずれかである。小児科医は小児の健康管理についての専門家でもあるので，小児科医が長期的・包括的にケアを調整するのが理想的である。患児の通常の健康管理，併発する疾患，心理的・社会的支援などにあたりながら，各専門医に紹介・コンサルトをしながら，連携して特別な治療を進めることができる。すなわち③の方法が患児にとっても，小児科医・専門医にとっても最良の方法といえる。

具体的な小児科医の役割として①成長・発達など総合的な評価を行う，②家族と一緒に短期的な目標を設ける，③予想される合併症やその症状を時期に応じて伝える，④各々の合併症以外の徴候・症状の訴えを聞き，適切な専門家との連携をとる，⑤母親の心配・不安を聞き，多種職で心理的支援を行えるように配慮する，⑥公費補助を含め社会的支援のため医療ソーシャルワーカー（MSW）等と協力して地域との連携を図ることである。

新生児科医は出生直後から児の治療にかかわ

り，家族との信頼関係を構築してきていることが多く，NICU 退院後の外来を担当することが多い。合併疾患の管理や心理的支援という面からも，継続してフォローアップする意義は家族にとって大きい。しかしながら，いつまで新生児科医によるフォローアップを継続するかについて一定の見解はないのが現状である。例えば，最も頻度の高い染色体異常である Down 症候群の場合，平均寿命は約 50 歳であること，心血管疾患や肥満，アルツハイマー病，視力・聴力障害など成人期の健康管理が快適な日常生活を送るための重要な課題であることなどを考慮すると，健康管理のコーディネーターとしての役割は，どの時点かで適切な医療者に移行されなければならない[5]。いつ頃，どこの医療機関への移行が最適なのかは個々の例で異なり，日本では保健医療体制として構築されていないのが現状である。

フォローアップで小児科医に必要とされる 疾患への理解

1. 正確な診断

染色体異常や先天異常症候群の児のフォローアップにあたって重要な点は，正確な診断を理解することである。比較的稀な異常や非典型的な徴候がいくつかみられるような場合，NICU 入院中に診断が確定されないままフォローアップされる場合もある。一方，近年の遺伝子解析の進歩により，次々と新しい「症候群」は書き加えられている現状で，先天性多発奇形症候群をできるだけ正確に診断するための情報収集は欠かせない。例えば，UR-DBMS（http://becomerich.lab.u-ryukyu.ac.jp/top.html）は，琉球大学医学部医科遺伝学（遺伝医学）により作成された奇形症候群を中心とする遺伝性疾患の総合データベースで，Syndrome Finder からは症状や所見から診断を推定することができる[6]。成書やウェブサイトを有効に使って正確な診断を行うことは児の健康管理以外にも，①遺伝に関する情報，②予後に関する予測，③適切な臨床検査，④治療や管理計画の優先事項の決定，⑤合併症のスクリーニングの計画，⑥将来の教育計画など，長期にわたって起こり得る問題の

解決のため，適宜必要な専門家との連携を図るためにも重要である。

2. 自然経過に関する情報

正確な診断と同様，その疾患や症候群の自然経過，子どもの成長や発達の経過，合併症の出現や進行の事実を知ることは必須である。医学的な側面のみならず，社会的側面（就学，就労など），日常生活活動に関する情報も含み，患者家族も必要とする情報である。当然，同じ疾患，症候群であっても，その自然経過は常に多様性があり，経過も個々に幅がある[7]。したがって，診断に基づき疾患の自然経過を理解した上で，実際の個々の症状に応じてフォローアップを行う必要がある。種々の染色体異常や奇形症候群の自然経過を検索するために，ウェブサイト，家族会からの情報などの活用は有用である。

3. 遺伝相談

先天異常が，何らかの染色体異常，あるいは遺伝子異常に起因するとわかった場合，両親・家族にとっては成長障害，知的障害，合併症などその児に起こり得る問題とともに，次の子どものこと，次世代への影響など遺伝子疾患といった意味での心配も出てくる。染色体異常や先天異常の発生についての一般的な説明も必要であり，それは初期診療を行う小児科医・新生児科医が行うことが多く，染色体異常，遺伝子異常について基礎的な理解が必須となる。しかし，解釈の難しい染色体異常や稀な遺伝子異常の疾患などで十分な理解が困難な場合，曖昧な情報提供や「情報がない」といってしまうのでは不安を助長してしまう[8]。このような場合，臨床遺伝専門医による遺伝カウンセリングへ，家族の希望にあわせたタイミングで紹介を行う。

患児や家族か必要とする支援

先天異常をもつ児の長期フォローアップを行う上で，小児科医は医療的側面以外に患児や家族が必要とする心理・社会的支援を行う役割をもつ[9]。各疾患の専門家と連携して複雑な治療を進める一