

総 説

HTLV-1 母子感染予防での小児保健関係者の役割

根路銘安仁

はじめに

HTLV-1 の感染と起因する疾患群への対策に総合的に取り組むため、2010 年 9 月に内閣総理大臣の指示により「HTLV-1 特命チーム」が設けられ、「HTLV-1 総合対策」が開始された。小児保健分野では、母子感染予防のために全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。それに伴い、医師向け手引き¹⁾および保健指導マニュアル²⁾が作成され、2017 年に厚生労働研究事業（代表 板橋家頭夫）により「HTLV-1 母子感染予防対策マニュアル」³⁾が作成された。

本年、前研究班でのコホート研究で短期母乳栄養法と完全人工栄養法を選択した場合に母子感染率に有意な差はなかったエビデンス^{4,5)}をうけて厚生労働科学研究（代表者 内丸薫）が 2022 年にマニュアル改訂を行った⁶⁾。今回の改訂でも人工栄養が最も確実な方法である。一方、短期母乳栄養は「母親が母乳を与えることを強く希望する場合」に限り選択肢として考慮することであったが、90 日未満で完全人工栄養に移行する支援を行うことで完全人工栄養とともに選択肢として含められることになった。短期母乳を選択するには支援する体制を整備することが必須である。短期母乳選択者への支援において小児保健関係者も産科医療施設、小児医療施設、行政機関に所属しており、連携するため互いの支援内容の理解を深める必要がある。

今回、マニュアル改訂を機会に HTLV-1 母子感染予防について概説する。

I. 我が国の HTLV-1 母子感染対策のあゆみ

1. HTLV-1 と母子感染対策の歴史

1977 年に高月清らにより成人 T 細胞白血病 (Adult T cell leukemia: ATL, 以後 ATL) が報告された⁷⁾。1981 年には日昭頼夫が ATL と関連するウイルスとして HTLV-1 を報告した⁸⁾。1985 年に日野茂男らが母乳を介した感染の成立を証明し、母子感染の対策のきっかけを作った⁹⁾。

HTLV-1 流行地域で、それぞれ率先して研究対策が行われ成果を上げてきた。長崎県では 1987 年には ATL ウイルス母子感染防止研究協力事業 (ATL Prevention Program Nagasaki: APP) を開始し現在まで継続している¹⁰⁾。鹿児島県でも 1985 年から鹿児島大学と共同研究を行い、短期母乳栄養法を確立し、1997 年から鹿児島 ATL 制圧 10 ヶ年計画を実施¹¹⁾して完全人工栄養法と短期母乳栄養法から選択することを臨床で確立した。しかし、1991 年に厚生省心身障害研究重松班でキャリア率の高い地域でのみの対策で十分であり、全国一律の検査や対策は必要ないと提言され¹²⁾、全国的な対策はとられることは無かった。

その後、20 年ほど全国的な研究対策は低迷したが、2009 年厚生労働科学研究山口班報告で、HTLV-1 キャリア（以降キャリア）が全国に拡散している事が明ら

かとなり¹³⁾, 研究者や患者団体等の働き掛けもあって, 「HTLV-1 総合対策」が開始され, 全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。

2. HTLV-1 に関連する疾病

HTLV-1 は, 関連する疾患は多くあるが, 主なものとして ATL, HTLV-1 関連脊髄症 (HTLV-1-associated myelopathy: HAM, 以降 HAM) があげられる。しかし, キャリアだからといって多くの人は発症せず, 妊娠出産で問題になることは少ない。

ATL は 40 歳以前の発症は珍しく, キャリアのうち年間 1,000 人に 1 人, 生涯で約 5% 発症するとされている¹⁴⁾。しかし, 最近では, 新薬の登場や骨髄移植により治療成績も改善されつつあるが, 発症すると予後不良であり寿命ロスを引き起こす疾患である。

HAM は, キャリアのうち生涯で約 0.25% 発症するとされている¹⁵⁾。歩行障害や膀胱直腸障害が緩徐に進行することが多く, 治療で進行することを遅らせることはできるが止めることはできず, 生活の質 (QOL) を損ね健康ロスを引き起こす疾患である。

このように, HTLV-1 は私たちの健康寿命を短くする原因になるため, 感染予防対策が重要である。

II. HTLV-1 感染経路と対策

HTLV-1 は B 型肝炎ウイルスやヒト免疫不全ウイルス (HIV) のように血漿中や体液中のウイルス自体で感染するのと異なり, 感染リンパ球が生きのまま体の中に入り自分の中のリンパ球と細胞同士の接触によりおこる。感染力は弱く, 主な感染経路は, 1 母子感染, 2 性行為による水平感染, および, 3 輸血や臓器移植による感染があげられる。

1. 母子感染

母子感染は, 1 年程度母乳を与えた場合の母子感染率は約 15-20% とされている。

i. 母乳以外を介した感染

これまでの研究より, 母乳を与えない完全人工栄養法でも約 3% 母子感染が成立する¹⁻⁵⁾。母乳以外を介した感染経路が考えられてきたが, 経胎盤感染の存在が示唆されている¹⁶⁾。この経路を防止する有効な手段は現在ない。

ii. 母乳を介した感染

母乳中には感染リンパ球が多く含まれる¹⁷⁾, 母乳を介した感染が証明され⁹⁾, 感染予防のため, 完全人工栄養法¹⁸⁾, 短期母乳栄養法¹⁹⁾, 凍結解凍母乳法²⁰⁾が行われてきた。わが国で初めてのコホート研究で, 短期母乳栄養法 2.3% (95% 信頼区間: 0.0-4.6%), 完全人工栄養法 6.4% (95% 信頼区間: 1.9-10.9%) と両者に統計学的な差は認められなかった⁴⁾。母乳以外を介した感染率を考慮すると母乳を介した感染は栄養法を選択することで防止することが可能であると考えられる。

2. 性行為による感染

精液中に多くの感染リンパ球が含まれており¹⁷⁾, 傷ついた粘膜に精液や血液のリンパ球が接触することで感染すると考えられている。男性から女性が優位な経路になる。献血者のデータから HTLV-1 陽転化割合は女性が 10 万人あたり 6.88 人, 男性が 10 万人あたり 2.29 人であった²¹⁾。この経路を防止するのは, HTLV-1 に限らず他の性行為感染症と同様に挙児希望無い場合には, エビデンスは乏しいがコンドームの使用が有効と考えられる。

3. 輸血, 臓器移植による感染

血液や臓器中の感染リンパ球を介しての感染である。1986 年以降献血での HTLV-1 抗体検査が実施されているため安全に輸血が可能である。2000 年以降, 臓器移植後早期に HAM を発症した症例が報告された²²⁾。キャリアをドナーとした移植には制限がある。

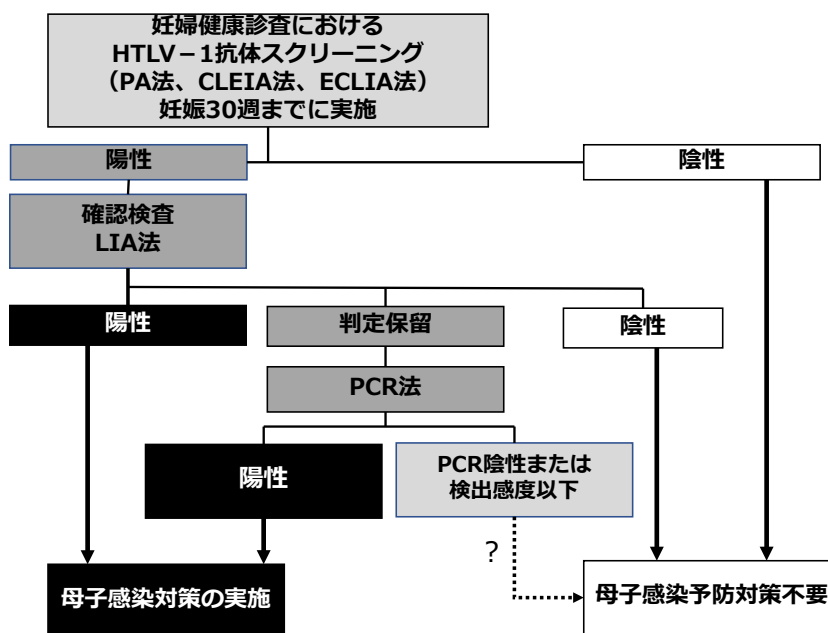
III. 母子感染対策での支援

1. 産科施設での支援 (妊婦健康診査でのスクリーニング検査から栄養法選択と達成まで)

i. スクリーニング検査からキャリアの確定まで (図 1)

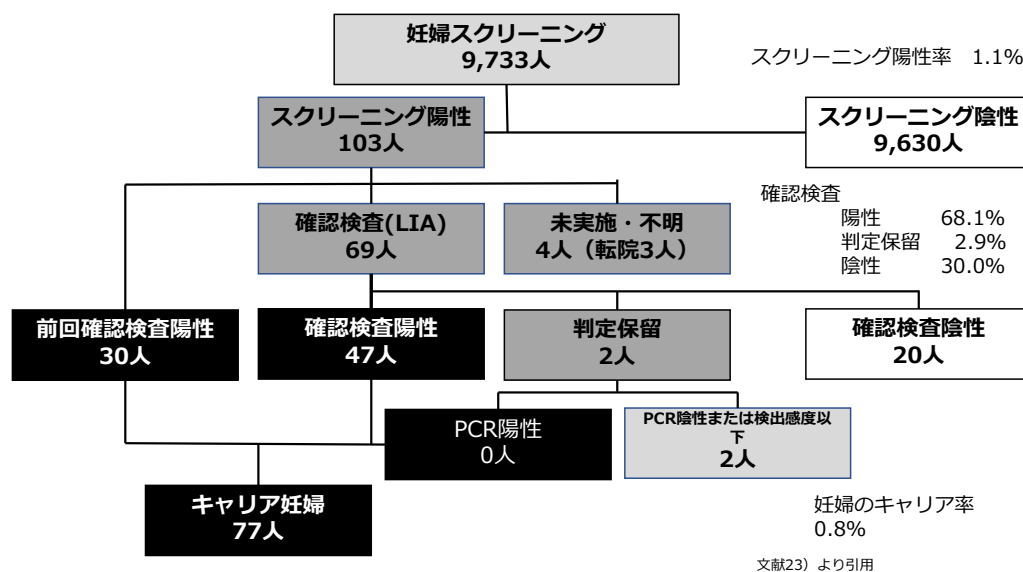
スクリーニング検査陽性の場合に確認検査をしなければキャリアであると判定できないことを伝え, ラインプロット (LIA) 法の確認検査を行う。流行地であった鹿児島でも 2018 年には, スクリーニング検査陽性者 69 人のうち確認検査での陽性者は 47 人 (68.1%) にとどまっている²³⁾ (図 2)。スクリーニング抗体が陽性で確認検査が陰性となる割合は, キャリアが少ない地域では高くなり, 非流行地域では 7 割以上陰性とも報告されている³⁾。

確認検査が陽性であればキャリアとして, 母子感染



文献6) より作成

図 1 妊婦健診における HTLV-1 抗体検査の流れ



文献23) より引用

図 2 鹿児島県における妊婦への HTLV-1 検査実施状況 (令和元年度)

対策を含め情報提供を行う。キャリアは児への感染防止と共に自身が将来発病する可能性で不安となるため²⁴⁾、心理的サポートを開始することが必要である。多くのキャリアマザーが相談できずに悩みを抱えている現状がある²⁵⁾ため、保健医療者から話しやすい環境を作っていくことが求められる。

一方、確認検査で「判定保留」となる確率は減ったが一定数存在する。2016年から「判定保留」であった妊婦に限り PCR 法が保険適用された。PCR 法で「陽性」であればキャリアとして扱う。「陰性もしくは検

出感度以下」の場合には母子感染の可能性は低いと推定されるがエビデンスが確立していない⁶⁾。授乳で感染症例もあった²⁶⁾ため、キャリアではないとはいえ対応が難しい。

ii. キャリアの確定から栄養法選択と達成への支援

キャリアであった場合、感染防止のため栄養法の選択を行う。十分な説明や栄養法選択の意志決定支援を受けた母親では、産後1か月、および3か月のエジンバラ産後うつ病評価尺度 (EPDS) は差を認めず、また EPDS が 9 点以上を示す割合も一般的な妊婦に比

	母乳	人工栄養（ミルク）
児	最適な成分組成で少ない代謝負担 感染症の発症および重症度の低下 小児期の肥満や2型糖尿病の発症リスクの低下 乳児突然死症候群のリスクが下がる 喘息やアトピー性皮膚炎のリスクの低下	ビタミンD,Kや鉄分などが不足しにくい
母親	産後の母体の回復の促進 衛生的、経済的で手間もかからない	父親も授乳に参加できる 授乳量が測定しやすい

図3 母乳と人工栄養（ミルク）の児と母親のメリット

栄養方法	完全人工栄養	短期母乳栄養（90日未満）	凍結解凍母乳栄養	長期母乳栄養
母子感染予防効果	母乳を介した母子感染を予防するためには最も確実な方法（母子感染率約3%）	完全人工栄養と比較して明らかな差がない達成できる環境では母子感染予防対策として推奨できる	エビデンスとしては少ない（早産児に対して考慮する）	母子感染率約15～20%。母子感染予防対策としては推奨されない
メリット	最も確実である	母乳のメリットをある程度得ることができる直接授乳が可能	母乳のメリットをある程度得ることができる母乳が出る限り与えることができる	母乳のメリットが得られる
デメリット	完全人工栄養購入費がかかる（約10万円）母乳のメリットが得られない直接授乳ができない	90日未満しか与えることができない完全人工栄養に90日未満で移行完了するのに困難がある助産師等の支援が必要である	バック購入費がかかる（約10万円）凍結解凍の手間がかかる直接授乳ができない	感染する確率が上がる

図4 各栄養法の母子感染予防効果とメリット・デメリット

べて高くなかったことから、十分な説明や支援が重要であると考えられる²⁷⁾。

母乳を介した感染を防ぐ意味では完全人工栄養法が最も確実である。しかし、母乳育児は母子ともに多くのメリットがある²⁸⁾（図3）。そのため短期母乳栄養法が検討され、コホート研究でのエビデンスより今回のマニュアル改訂で短期母乳栄養法も選択肢として含むことになった⁶⁾。また、凍結解凍母乳栄養法も検討されたが、症例数が少なくエビデンスが不十分とし選択肢には含まれなかったが早期産児などが選択する可能性がある。母子感染予防よりも母乳栄養のメリットから長期母乳栄養法を選択する母親も存在する。母親および家族が何を重視するかによって選択肢は変わってくる。

そのため保健医療従事者は、自身の価値観にとらわれることなく、感染防止についての情報と共に、各栄養法のメリットと困難さなどのデメリットの情報（図4）を提供し、母親と家族から何を重視するかを聞いて、どの栄養法を選択するか意思決定支援をおこなう。

どの栄養法を選択しても母親は選択後も自分の選択が正しかったのかと揺れ動いている。出産まではいつでも変更できることを伝える。出産後は栄養法変更が難しいため、正しい選択であったと支持的な対応を行い、選択した栄養方法を達成できるように支援を行う。栄養法を実施するにあたり、選択栄養法によらず約3

割が困難を抱えていた²⁹⁾。

選択をするにあたり、出生時に児の検査を行い感染していたら母乳を与えたいという希望があることもある。抗体検査は移行抗体により陽性となり、PCR検査も陰性であっても感染する可能性があるため出生時に検査での判断はできない。

a. 完全人工栄養法

困難を感じた理由の多くは「周囲の理解不足」だった²⁹⁾。産婦人科外来には、母乳育児を推奨するポスターも多く、母親学級で授乳指導や出産後授乳する人との同室などがストレスであった。産科スタッフはそのようなストレスがあることを知り配慮することが望まれる。

また、退院後にキャリアであることを知らない人から「母乳がでないの？」といわれストレスだったと言うこともあったため、一般の方への啓発活動が重要であるが難しい。せめて身近な人から言われぬように、キャリアであることをどこまで伝えるかも栄養法選択と共に相談して決めていくことが必要である。栄養法選択時点では伝えることができなくても、出産後に関係性をつくり家族の理解と協力を得られるように母親の気持ちに寄り添いながら支援することも重要である。

一方、完全人工栄養法と決定していた場合に早産となった場合、壊死性腸炎の予防などで母乳を与えることを検討することがある。早産児に人工栄養を与えての壊死性腸炎発症など生命リスクと、凍結母乳栄養

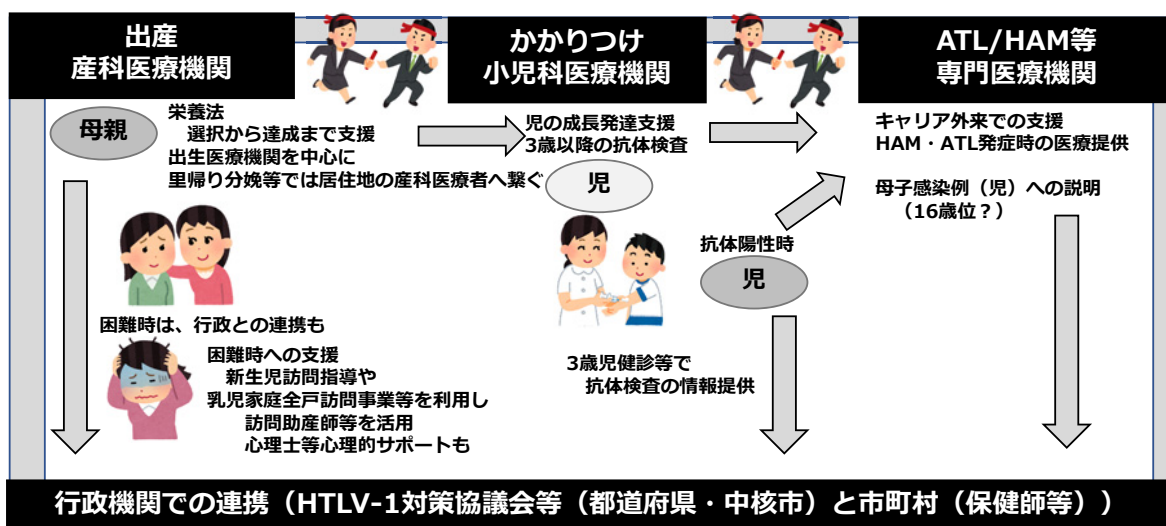


図 5 母子保健分野での医療機関および行政支援体制

法のエビデンスは少ないが理論的には HTLV-1 感染のリスクをよく説明して母親に納得の上、選択してもらう。

b. 短期母乳栄養法

本栄養法の困難は、やはり 90 日未満で人工栄養への完全な移行の達成である。ひとりで達成するのは困難で、支援が無ければ 5 人に 1 人やめられない可能性がある⁴⁾。その理由は乳房トラブルなど技術的支援不足であった²⁹⁾。産後 1 か月健診で支援が途切れていることが多かったが、鹿児島県では短期母乳栄養法を選択した場合に、約半数が「3 か月後の断乳を確認した」と回答していた²³⁾。出産した産科施設で母親も慣れているため 1 か月以降も継続して、人工栄養への完全移行達成の確認まで支援を続けるのが望ましい。もしも、里帰り分娩等の場合で難しい場合には、本人の同意のもと居住地近くの産科医療機関や開業助産師へ紹介するか、居住地の保健師につなぎ、新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）で助産師の活用を依頼することを検討し、途切れることがない支援体制を作る。

また、「そんなに泣くならあげたら」と夫に言われ心が折れたと話す方もいたので、移行時に家族の支援も重要であり、理解と協力が得られるように事前に話し合いを持ち準備しておくことが重要である。移行後は、完全人工栄養と同じように他者からの授乳に関するストレスは生じうる。

完全人工栄養法も含め短期母乳栄養法も移行後、約 1 年間で人工栄養購入費が 10 万円ほどかかる。経済

的理由から長期母乳を選択する家族もいた。鹿児島県では 2019 年以降の一部助成が行われている³⁰⁾。健康社会格差解消のために HTLV-1 キャリアだけでなく、本人の意思によらない理由で母乳を与えることができない方への支援を検討する必要がある。

c. その他の栄養法

母親と家族に説明後、十分考え抜いた末に「長期母乳栄養法」や「凍結母乳栄養法」を選択することもある。自身がアレルギー体質で悩んでこられ、母乳をあげないことで HTLV-1 関連疾病の発症するリスクと母乳をあげることでのアレルギー発症のリスク軽減から、長期母乳栄養法を選択された母親がいた。絶対に正しい栄養法はなく、本人の価値観により正しい選択肢は変わってくる。本人が納得できる選択をした際に達成できるよう支援することが重要である。

iii. 切れ目ない支援へ (図 5)

2010 年に妊婦スクリーニング検査が開始後、産科施設での支援は充実してきている。しかし、産後 1 か月健診以降は途切れること²³⁾の課題がある。そのため、次項にある小児医療施設での支援と行政機関での支援に診療情報提供書等をつないでいく。母体・児の一般的な情報以外に、抗体検査の情報、選択栄養法、キャリアであることを知っている家族の範囲が有効な情報になる。

2. 小児医療施設での支援 (産科医療施設からの紹介から内科医療施設紹介まで) (図 5)

キャリア妊婦より出生した児を産科医療機関等から

の紹介を受ける。小児期において南米で HTLV-1 関連の神経症状³¹⁾や皮膚症状³²⁾の報告があるが、我が国ではほぼ報告がない。人種差なのかその差を説明する要因は不明である。他の小児と同じように定期予防接種や健診をすすめていくが、母子感染の有無の確認についての説明が必要になる。

母子感染の確認は、3歳以降に妊婦健診と同様の方法でスクリーニング検査を実施する。移行抗体消失後3歳までに抗体が陽転することから³³⁾、それ以前に検査して陰性であってもその後陽性になる可能性があるため、勧められない。

3歳以降に検査を実施すれば、約97%の確率で母子感染していなかったと判断できる。母親も自分が行った感染対策の成果があったことを確認でき満足度も高く、母親の不安を取るという大きなメリットがある。しかし、母乳以外の経路での感染が約3%あり、母子感染したことを知った母親のショックは大きい。十分なカウンセリングと児が理解できる年齢に達したときに、告知と情報提供の機会を確保する必要がある。HTLV-1は妊娠・母乳をあげる・性行為・臓器移植など特別な関係での行為以外の日常生活で他の人に感染させることはないため、性活動期が始まるまでは特別な感染防止策は必要ない。そのため児の所属する施設・学校等へのキャリアであることの情報提供は必要ない。

児がキャリアであることを知るメリットは、性活動期前に男女ともパートナーを守るために HTLV-1 に限らず性感染予防のためにコンドームの使用の重要性の教育、女性は妊娠後限られた時間ではなく事前に情報を得て判断する時間の確保ができることが考えられる。偶発的に児が感染を知る機会として献血がある。献血時希望すれば HTLV-1 感染には親展郵便で通知される³⁴⁾。著者の経験であるが妊婦健診で分かる前に、1割ほどが献血で既に知っていた。しかし、多くは同封の資料では理解できず、かつ親を含め誰にも相談せず一人で悩み、中には HIV と勘違いして自殺を考えたものがいたため、事前に告知し説明する機会を確保することができるのはメリットになるかもしれない。しかし、HTLV-1 に関しての国民の理解が十分でないためキャリアへの負担が多く、3歳時に検査をして陽性であればその後に告知を行うことは、約3%と少数ではあるが「知らされない」という児の自己選択権を侵害する可能性もあり、判断が難しい。

3歳児に理解して自己決定してもらうことが難しいため、一つの方法として本人が HTLV-1 感染のことを理解できるようになった時、目安として性活動期が活発化や献血をすることができる16歳よりも前に、「母親がキャリアであり、子どものことを考えて栄養法を選択した」、「その栄養法を選択しても、一定の割合で母子感染してしまう」、「検査でキャリアであるかは知ることができる」、「キャリアである場合には性行為の際にコンドームの使用でパートナーに感染するのを減らすことができる」、「将来子どもに関しては栄養法を選択することで母子感染リスクを下げるができる」等の事柄を伝え、児に選択してもらう方法もあると考える。母子感染の有無の確認の検査は、母親および家族の価値観で検査の時期、実施するかしないかを決めることになる。

母子感染予防のため栄養法を達成した後、安堵と共に自身がキャリアであることの不安が再度湧き上がってくることもある。日本 HTLV-1 学会では登録医療機関制度を設けて、HTLV-1に関連した相談対応が可能な施設を認定して公開している³⁵⁾。2021年5月時点で16機関中九州・沖縄に10機関と偏在しているが、現在も登録募集を行っているので今後増えていくことが期待される。また、登録されている医療機関がない場合には、厚生労働省は各都道府県や政令指定都市に対して、HTLV-1母子感染対策協議会を設置し体制整備を推進している³⁶⁾ので、問い合わせてみるとよい。

3. 行政機関（各都道府県や政令指定都市、市町村）での支援（医療機関との連携）(図5)

各都道府県や政令指定都市は HTLV-1 母子感染対策協議会を設置し、妊婦に対する HTLV-1 抗体検査の適切な実施、相談窓口、母子感染に関する普及啓発、医療機関連携、体制整備、評価などを行うことになっている。産科医療機関でキャリアと判明した場合には、本人の同意を得て、富山県³⁷⁾をはじめ未熟児等出生連絡票を用いたり、鹿児島県³⁸⁾のように専用の情報提供書を用いたりして連携をとっている地域もある。

各都道府県や政令指定都市は、自治体内の出生数と妊婦の感染率から、年間のキャリア妊婦の数、母子感染者数、将来の発症者数を推定し母子感染対策の体制整備が必要である。例えば、鹿児島県では令和元年度11,977出生数で感染率が0.8%から、年間のキャリア妊婦の数は約100人、3年後の母子感染者は3人、

HTLV-1 関連疾患の発症者は 5 人と推定される。流行地であった鹿児島県でも数が減っているため、非流行地域では更に少ないと考えられる。そのため各都道府県や政令指定都市を中心とした整備が重要である。

産科医療機関より情報提供があった際には、市町村の保健師による支援を行う。新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）など既存の事業を利用し、短期母乳栄養法で乳房のことで不安を抱えている場合には助産師など産科医療関係者、心理的な不安に関しては臨床心理士など精神医療関係者など専門職を活用し、必要なサービスにつなげる。

3 歳児健診時には、3 歳以降検査が可能であり、そのメリット・デメリットを含め情報提供を行い、母親および家族の選択を支援する。決して検査実施を強制してはならない。また、キャリアであることへの不安や母子感染した症例やキャリアである母親を各都道府県や政令指定都市が整備したカウンセリングや診療体制へ適切につなぐことも必要である。

おわりに

HTLV-1 総合対策として全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになり 10 年が経過した。産科医療施設での支援体制は整備されつつあるが、今回のマニュアル改訂で短期母乳栄養法選択者への支援を新たに整備する必要がある。今後、小児保健関係者は所属機関は異なっても互いの支援内容を理解し、産科医療施設から小児医療施設、内科等専門医療施設への医療機関同士の連携、また都道府県と市町村の行政機関内同士での連携を行うことが求められる。医療機関と行政機関を中心に社会での総合的な HTLV-1 キャリア支援を多方面から行うことで、キャリアマザーと児が脱落しない体制が構築されることを期待したい。

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EDITED BY

Wei Zhang,
University of Minnesota Twin Cities,
United States

REVIEWED BY

Yorifumi Satou,
Kumamoto University,
Japan
Philippe V. Afonso,
Institut Pasteur,
France

*CORRESPONDENCE

Kiyonori Miura
kiyonori@nagasaki-u.ac.jp

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Frequency of HTLV-1 seroconversion between pregnancies in Nagasaki, Japan, 2011–2018

Nahoko Komatsu¹, Masako Iwanaga², Yuri Hasegawa¹, Shoko Miura¹, Naoki Fuchi¹, Hiroyuki Moriuchi³, Katsunori Yanagihara⁴ and Kiyonori Miura^{1*}

¹Department of Obstetrics and Gynecology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, ²Department of Clinical Epidemiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, ³Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, ⁴Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background: Human T-cell leukemia virus type-1 (HTLV-1) is transmitted vertically from an infected mother to her child *via* breastfeeding during infancy or horizontally *via* sexual contact. However, little information is available on the HTLV-1 seroconversion rate in pregnant mothers and the impact of new HTLV-1 infection on mothers and babies during the perinatal period.

Methods: From the database of a prefecture-wide antenatal adult T-cell leukemia prevention program in Nagasaki, Japan, we extracted data on 57,323 pregnant women who were screened for anti-HTLV-1 antibody during 2011–2018. Data on the 16,863 subjects whose HTLV-1 proviral load (PVL) was measured more than twice were included in our analyses.

Results: In total, 133 (0.79%) pregnant women were HTLV-1-positive during their first pregnancy and nine (0.05%) seroconverted before or during subsequent pregnancies (between pregnancies). The median PVL (per 100 peripheral blood mononuclear cells) was significantly lower in the seroconverted mothers (0.10%) than in the initially seropositive mothers (0.15%). A repeated measures correlation analysis for the individual PVLs of the HTLV-1-positive pregnant women showed that PVL increased with parity number ($r_{rm}=0.25$) with no perinatal problems.

Conclusion: The HTLV-1 seroconversion rate between pregnancies was 0.05%, and their HTLV-1 PVL increased annually but no perinatal problems were noted.

KEYWORDS

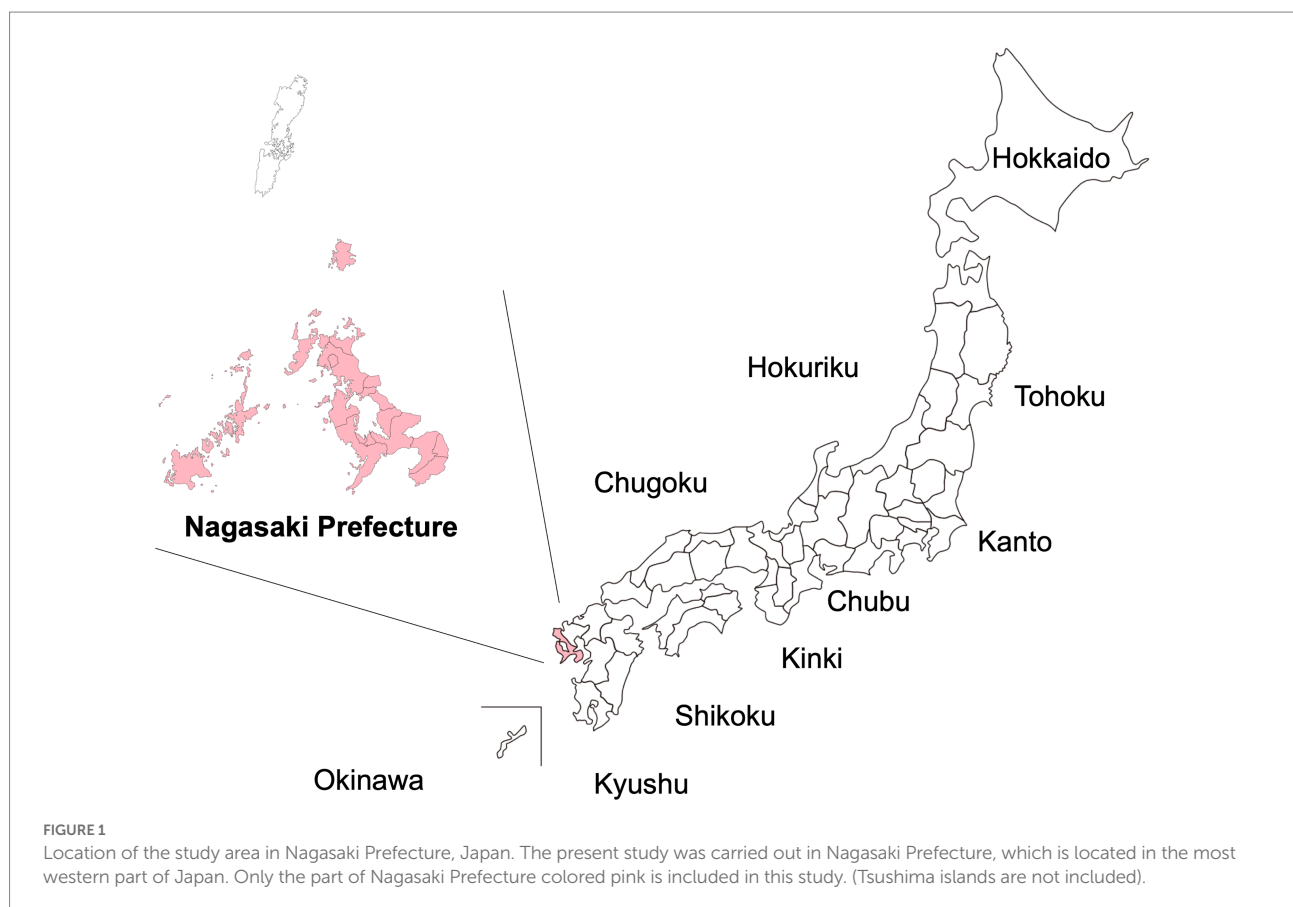
HTLV-1, pregnant woman, carrier, screening test, seroconversion, horizontal transmission, proviral load, adult T-cell leukemia-lymphoma

Introduction

Human T-cell leukemia virus-1 (HTLV-1) is a retrovirus that causes adult T-cell leukemia (ATL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and a variety of HTLV-1-associated inflammatory disorders (Watanabe, 1997). Globally, HTLV-1 infects at least 5–10 million people (Gessain and Cassar, 2012), particularly in southwest Japan, Brazil, the Caribbean islands, Central and South America, sub-Saharan Africa, and central Australia (Gessain and Cassar, 2012; World Health Organization, 2020). HTLV-1 infects mainly CD4-positive T-cells and is known to transmit from person-to-person *via* cell-to-cell contact between HTLV-1-infected cells and uninfected cells through three modes (Bangham, 2003; Matsuoka and Jeang, 2007; Pique and Jones, 2012): vertical mother-to-child transmission from HTLV-1-infected mothers *via* breastfeeding (Hino et al., 1985), horizontal transmission from HTLV-1-infected partners *via* sexual intercourse (Stuver et al., 1993; Kaplan et al., 1996; Roucoux et al., 2005; Satake et al., 2016; Paiva et al., 2017), and iatrogenic transmission *via* HTLV-1-infected donated blood or organs. However, the risk of iatrogenic transmission through transfusion can be reduced by performing leukoreduction prior to transfusion (Okochi et al., 1984; Armstrong et al., 2012).

The first scientific evidence of vertical transmission from a HTLV-1-infected mother to their infant *via* prolonged

breastfeeding by the infected mother was presented in 1985 by researchers from Nagasaki University, located in southwest Japan (Hino et al., 1985; Figure 1). They presented the following findings: (1) the first nationwide survey of HTLV-1 infection in Japan identified Nagasaki Prefecture as one of the regions with the highest prevalence of HTLV-1-infected individuals (Tajima et al., 1982); (2) HTLV-1-infected cells are present in breastmilk from HTLV-1-carrier mothers, and infection through breastfeeding is associated with a higher probability of developing ATL (Kinoshita et al., 1984); and (3) experimentally, HTLV-1 can be transmitted *via* intraoral inoculation among common marmosets (Kinoshita et al., 1985; Yamanouchi et al., 1985). Soon after, a prefecture-wide, multidisciplinary, antenatal intervention program, known as the “ATL Prevention Program (APP),” was established in 1987 in Nagasaki (APP Nagasaki; Hino et al., 1987) through collaboration with virologists, obstetric gynecologists, hematologists, pediatricians, and clinical laboratory scientists at Nagasaki University, obstetric gynecologists throughout Nagasaki Prefecture, and public health officers of the Maternal and Child Health Division (MCHD) of the Nagasaki Prefectural Government. The purpose of APP Nagasaki was to reduce the vertical transmission of HTLV-1 *via* breastfeeding and to reduce the future development of HTLV-1-associated diseases through systematic screening for anti-HTLV-1 antibodies in pregnant women and the avoidance



of breastfeeding in identified HTLV-1-infected mothers, in Nagasaki Prefecture.

As previously reported, APP Nagasaki led to a marked reduction in mother-to-child HTLV-1 transmission rates from 20.5% before the APP began to 2.4% after its implementation (Hino et al., 1997; Katamine, 1999; Hino, 2011; Moriuchi et al., 2013; Miura and Masuzaki, 2017). Other intervention programs similar to APP Nagasaki have been implemented in several areas endemic for HTLV-1 in Japan (Takahashi et al., 1991; Kashiwagi et al., 2004). However, HTLV-1 infection is currently widespread across geographical regions (Watanabe, 2011; Satake et al., 2012), and the number of HTLV-1 carriers in the metropolitan areas in Japan has increased. This situation probably reflects the migration of individuals from HTLV-1-endemic areas (Watanabe, 2011). A nationwide antenatal screening program for HTLV-1 was introduced in Japan in 2011 (Itabashi et al., 2020). Currently, it is estimated that each year ~1,600 HTLV-1-infected pregnant mothers in Japan (almost 0.16% of all pregnant mothers in Japan; Suzuki et al., 2014) are recommended to refrain from breastfeeding to avoid mother-to-child HTLV-1 transmission by methods similar to that of APP Nagasaki.

Recently, researchers from APP Nagasaki reported that the HTLV-1 proviral load (PVL), induced regulatory T-cell population, and soluble interleukin-2 receptor (sIL-2R) levels of HTLV-1-infected pregnant mothers remained stable during pregnancy but became elevated after delivery (Fuchi et al., 2018). However, many questions regarding the impact of HTLV-1 infection on pregnant mothers remain unanswered. For example, the number of pregnant mothers who seroconvert from HTLV-1 negative to positive between pregnancies, how the HTLV-1 PVL changes in HTLV-1-infected pregnant mothers through delivery (between pregnancies), and the specific risks to pregnancy outcomes for HTLV-1-infected and HTLV-1-seroconverted mothers are not currently known.

The present study therefore aimed to assess the HTLV-1 seroconversion status in multiparous mothers who participated in APP Nagasaki, the individual changes of the HTLV-1 PVL between pregnancies in HTLV-1-positive mothers, and the impact of HTLV-1 positivity on pregnancy outcomes.

Materials and methods

Study area and database

From its initiation in July 1987 to April 2018, the APP Nagasaki database included information on ~330,000 pregnant mothers, from almost all areas of Nagasaki Prefecture, who were tested for HTLV-1 infection (Figure 1). The database is managed by the Department of Obstetrics–Gynecology at Nagasaki University Hospital (Miura and Masuzaki, 2017).

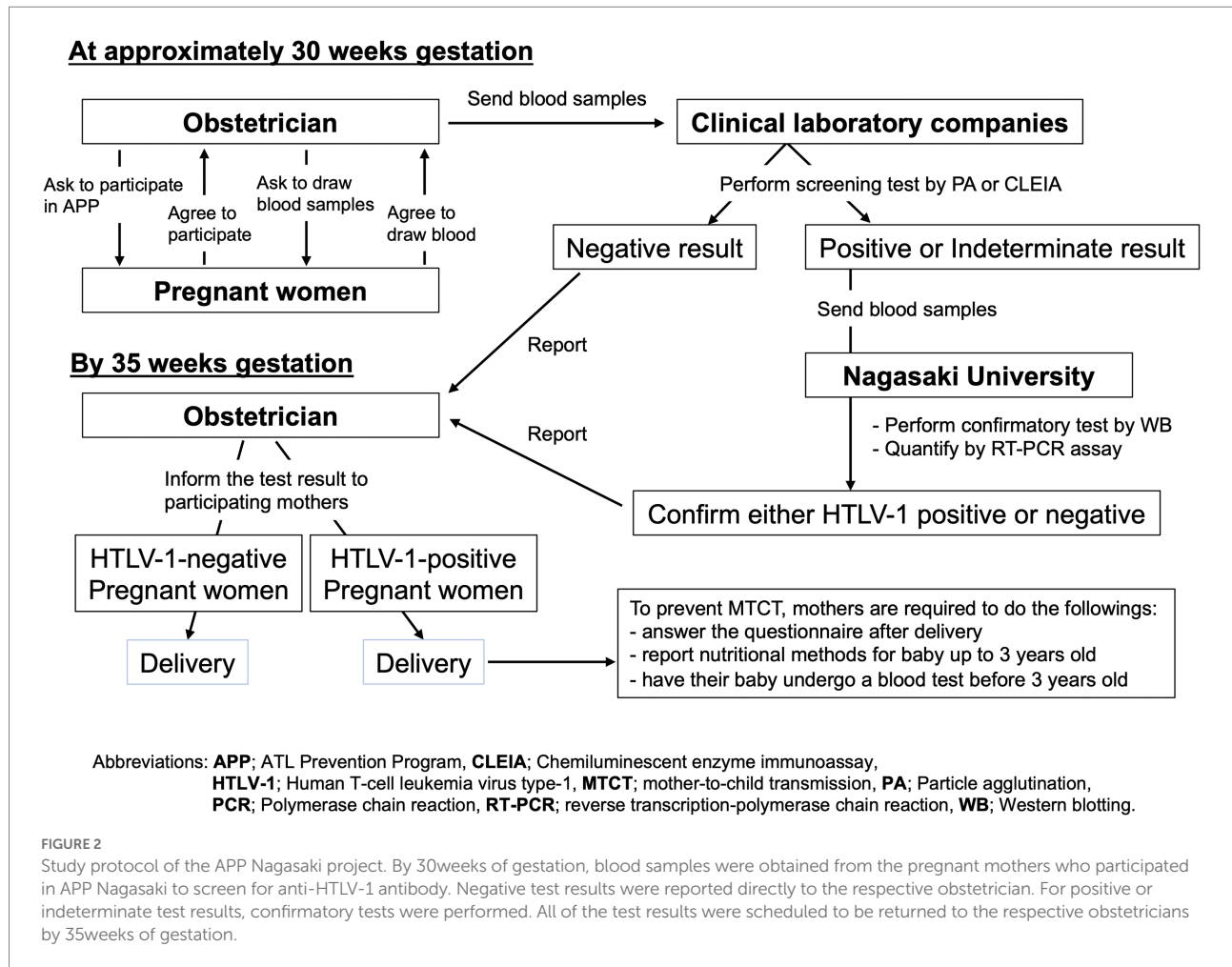
Protocol employed for APP Nagasaki

Figure 2 shows the protocol employed for APP Nagasaki (Miura and Masuzaki, 2017). Briefly, any pregnant mothers who were ~30 weeks of gestation and living in most areas of Nagasaki Prefecture were asked to participate in APP Nagasaki when visiting their obstetric gynecologists. After providing consent to participate in the project, each pregnant mother was required to provide a blood sample for an anti-HTLV-1 antibody test. From 2011 onwards, such blood samples were sent to one of five commercial clinical laboratory companies (see Acknowledgment) where a screening test for anti-HTLV-1 antibody was performed using either a particle agglutination (PA) assay, a chemiluminescent immunoassay (CLIA), or a chemiluminescent enzyme immunoassay (CLEIA). The definition of “HTLV-1-positive” as a result of the screening test is a titer of 8 or higher in the PA assay or a cutoff index (COI) of ≥ 1.0 in the CLEIA or CLIA, in accordance with the manufacturer’s criteria (Fujirebio, Japan).

All of the negative screening test results from the clinical laboratory companies were sent back to the respective obstetric gynecologists, for them to inform the respective pregnant mothers. From 2011 onward, in the case of a positive or suspected positive screening test result, the residual blood sample was forwarded to the APP Nagasaki office at Nagasaki University Hospital where a confirmatory test was performed by western blotting and the HTLV-1 PVL was quantified by a real-time polymerase chain reaction (RT-PCR) assay in the Department of Laboratory Medicine. The final test results were reported to the respective obstetric gynecologists, who then informed the respective mothers by 35 weeks of gestation (Figure 2). The obstetric gynecologists also asked their public health nurses to explain to HTLV-1-positive pregnant mothers how to prevent HTLV-1 mother-to-child transmission, preferentially through exclusive bottle-feeding or alternatively by freeze–thawing breast milk or only short-term breastfeeding for no more than 3 months. According to the APP Nagasaki report, the majority of HTLV-1-positive pregnant mothers chose the first choice option of exclusive bottle-feeding to prevent mother-to-child transmission (Miura and Masuzaki, 2017).

Quantification of the HTLV-1 PVL

In APP Nagasaki, a quantitative RT-PCR assay was routinely performed from 2011 onward to quantify the HTLV-1 PVL in peripheral blood mononuclear cells (PBMCs) from anti-HTLV-1 antibody-positive pregnant mothers and those with indeterminate western blotting results. The details of the method used to quantify the HTLV-1 PVL have been previously published (Kamihira et al., 2003; Sasaki et al., 2010), and the resulting value was expressed as the copy number per 100 PBMCs. All measurements were performed by the Department of Laboratory Medicine at Nagasaki University Hospital. Coefficient variation (CV) of HTLV-1



quantitative PCR test in Nagasaki university hospital was 13.3% (Kuramitsu et al., 2015).

Questionnaires for HTLV-1-positive mothers and their doctors after delivery

Within 1 week of delivery, each of the HTLV-1-positive mothers who participated in APP Nagasaki was required to answer questions about their birthplace, pregnancy history, the feeding method chosen by their own mother (i.e., the grandmother) during their infancy, and the feeding method that they chose for their own baby. Their obstetric gynecologist was also required to answer questions regarding pregnancy/delivery complications, the health condition of the baby, and the medical history of the pregnant mother (Supplementary material S1).

Data extraction for analysis

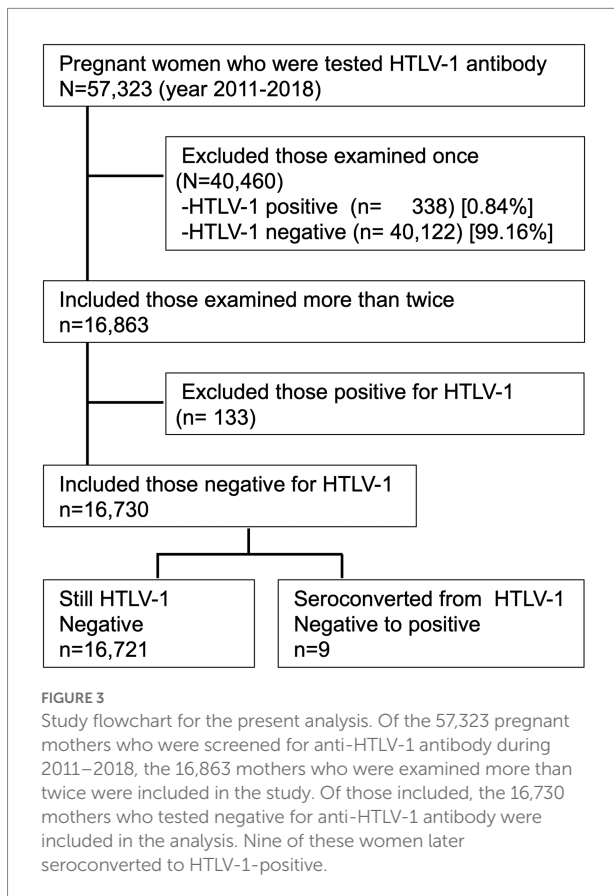
The dataset used for analysis in this study was extracted from the APP Nagasaki database after obtaining approval

from the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The APP Nagasaki was initiated in 1987, and modern techniques to measure the HTLV-1 PVL using an RT-PCR assay have been applied to participating mothers only since 2011 (Kamihira et al., 2003; Sasaki et al., 2010). Therefore, for the present analysis, we limited our data extraction to the years 2011–2018.

Statistical analysis

We analyzed the available data on pregnant mothers who were tested for HTLV-1 infection at least twice during pregnancy. The demographic data were summarized with standard descriptive statistics, such as frequencies (percentages) for categorical variables, and median (min–max) or median (interquartile range, IQR) values for continuous variables. The pregnant mother age at enrollment in the APP was treated as a continuous variable or categorized into four groups (<25, 26–30, 31–35, and >36 years old). The

method of feeding that the pregnant mothers themselves received from their own mothers was categorized into three groups: long-term breastfeeding (6 months or longer), short-term breastfeeding (shorter than 6 months), and formula feeding alone. The mothers were also categorized into subgroups based on their history of gravidity (the number of pregnancies), parity (the number of live births), and divorce. Continuous variables were compared using Wilcoxon rank-sum tests. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. All of the basic statistical analyses were performed using OpenEpi Statistical Software version 3.01 (<http://www.openepi.com>, Atlanta, GA, United States; Sullivan and Dean, 2009) and R package version 3.4.2 (R-Project for Statistical Computing, <https://CRAN.R-project.org>). To analyze changes over time in the HTLV-1 PVL by age and by parity of the HTLV-1-positive mothers, we conducted repeated measures correlation (rmcorr) analyses using the R package version 0.3.0 (R-Project for Statistical Computing, <https://CRAN.R-project.org>; Bakdash and Marusich, 2017) and calculated the correlation coefficient for repeated measures (*rrm*). All statistical tests were performed at the two-tailed 5% level of significance.



Results

HTLV-1 seropositive status

Figure 3 shows the flowchart for the present analysis. In the years 2011–2018, a total of 57,323 pregnant mothers were screened for anti-HTLV-1 antibody, and 471 (seropositive rate of ~0.82%) were identified as being HTLV-1-positive. Among the 57,323 screened women, 40,460 (70.6%) were examined only once, and the remaining 16,863 (29.4%) were examined more than twice. Of those examined only once, 338 (0.84%) were HTLV-1-positive; of those examined more than twice, 133 (0.79%) were HTLV-1-positive. Among the 133 HTLV-1-positive pregnant mothers screened during their first pregnancy, 61 (45.9%) had already been diagnosed as asymptomatic HTLV-1 carriers in a hospital before their enrollment with APP Nagasaki, but the remaining 72 had no prior HTLV-1 diagnosis information. To date, there have been no reports about ATL, HAM/TSP, or other HTLV-1-associated diseases from their obstetric gynecologists.

HTLV-1 seroconversion rate

During the period between January 2011 and December 2018, nine (0.054%) of the 16,730 pregnant mothers who were found to be negative for HTLV-1 during the initial screening subsequently seroconverted to HTLV-1 positive (Figure 3). Thus, the incidence rate of HTLV-1 seroconversion among HTLV-1-negative pregnant mothers was 17.5 (95% confidence interval: 11.4–26.0) per 100,000 person-years at follow-up.

Background characteristics

Table 1 summarizes the characteristics of pregnant mothers who were already known to be HTLV-1 seropositive before their entry into the study ($n=133$) and those of mothers who were HTLV-1 seronegative at study entry but later seroconverted to anti-HTLV-1 antibody-positive ($n=9$). The median age at first entry to APP Nagasaki was 30 years old (range, 17–47 years old) in mothers of known HTLV-1-seropositive status and 31 years old (range, 23–38 years old) in HTLV-1-seroconverted mothers. Although there was no statistically significant difference in the age distribution between the two groups, approximately half of those already known to be HTLV-1-seropositive were in their late 20s at their first pregnancy, whereas approximately half of the HTLV-1-seroconverted mothers were in their 30s at their first pregnancy. There was also no significant difference in the proportions of mothers with a family history of ATL, a divorce history, or particular screening test values or in the proportion of western blot-positive or -indeterminate individuals between the two groups.

In contrast, there were significant differences between the two groups regarding the feeding method that the participating

TABLE 1 The characteristics of HTLV-1-positive or HTLV-1-seroconverted pregnant women.

Characteristic	Mothers HTLV-1-positive at first pregnancy (n = 133)	Mothers seroconverted to HTLV-1-positive (n = 9)	p-Value
Age (year) at entry to APP Nagasaki			
Median (min, max), year	30 (17, 41)	31 (23, 38)	0.42
Age category, n (%)			
<25	19 (14.3)	2 (22.2)	
26–30	58 (43.6)	1 (11.1)	
31–35	44 (33.1)	5 (55.6)	
>36	12 (9.0)	1 (11.1)	
Nutrition method that participant mothers received from their mothers, n (%); [unknown = 22]			
Long-term breastfeeding	85 (63.9)	4 (44.4)	
Short-term breastfeeding	14 (10.5)	2 (22.2)	
Formula feeding	14 (10.5)	1 (11.1)	
Family history of ATL, n (%)			
Yes	9 (6.8)	1 (11.1)	
No	124 (93.2)	8 (88.9)	
Gravidity history, n (%); [unknown = 6]			
Once	61 (45.9)	0	
Twice	39 (29.3)	3 (15.8)	
Three or more	27 (20.3)	6 (31.6)	
Parity history, n (%); [unknown = 5]			
Once	76 (59.4)	0	
Twice	36 (28.1)	4 (44.4)	
Three or more	16 (12.5)	5 (55.6)	
Divorce history, n (%)			
Yes	10 (7.5)	1 (11.1)	
No	123 (92.5)	8 (88.9)	
Screening test values			
PA, titer	1,024 (16–8,192)	1,024 (16–8,193)	0.69
CLEIA, COI	34.4 (2.5–45)	34.4 (2.5–46)	0.47
WB test result, n (%); [unknown = 53]			
Positive	72 (90)	8 (88.9)	0.99
Indeterminate	8 (10)	1 (11.1)	
Quantified PVL, % per 1,000 PBMCs			
Median (min, max)	0.15 (0–7.05)	0.10 (0–1.09)	0.024

HTLV-1, human T-cell leukemia virus-1; APP, ATL Prevention Program; PA, particle agglutination; CLEIA, chemiluminescent enzyme immunoassay; COI, cutoff index; PVL, proviral load; PBMCs, peripheral blood mononuclear cells.

mothers themselves received from their mothers (i.e., the grandmothers), gravidity history, parity history, and HTLV-1 PVL. In brief, compared with the group of those already known to be HTLV-1-positive before pregnancy, the group of mothers that underwent HTLV-1 seroconversion between pregnancies had lower HTLV-1 PVL (0.15% vs. 0.10% per 100 PBMCs; $p < 0.024$).

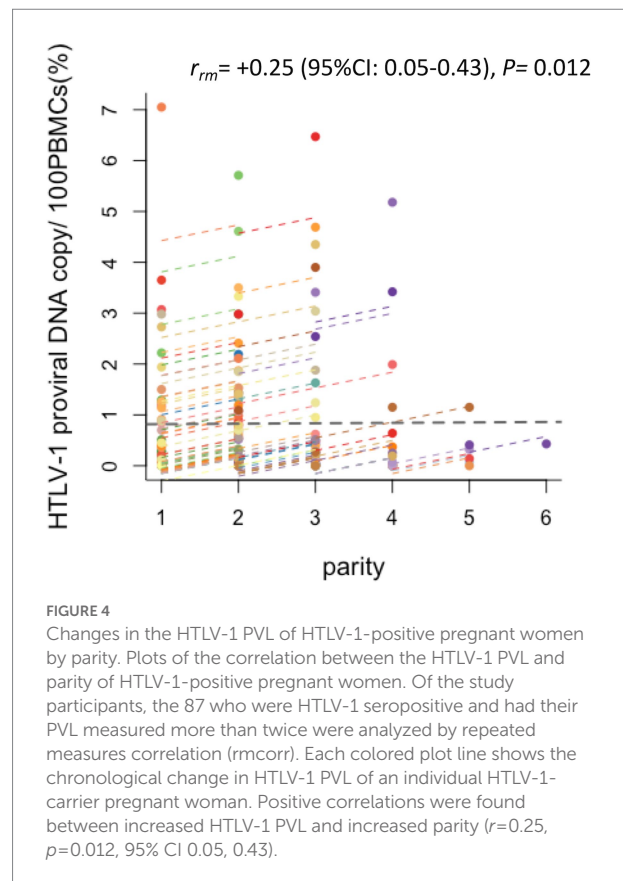


FIGURE 4

Changes in the HTLV-1 PVL of HTLV-1-positive pregnant women by parity. Plots of the correlation between the HTLV-1 PVL and parity of HTLV-1-positive pregnant women. Of the study participants, the 87 who were HTLV-1 seropositive and had their PVL measured more than twice were analyzed by repeated measures correlation (rmcorr). Each colored plot line shows the chronological change in HTLV-1 PVL of an individual HTLV-1-carrier pregnant woman. Positive correlations were found between increased HTLV-1 PVL and increased parity ($r = 0.25$, $p = 0.012$, 95% CI 0.05, 0.43).

Regarding whether the mothers had known about the HTLV-1 infection status of their husband or sexual partner, only two pregnant mothers reported HTLV-1 infection in their partner; the rest of the study participants did not know their partner's HTLV-1 infection status.

Sequential changes in the HTLV-1 PVL in HTLV-1-positive pregnant mothers

An analysis of the HTLV-1-positive mothers revealed a statistically significant positive correlation between an increase in parity number and an increase in HTLV-1 PVL ($r_{rm} = +0.25$, $p = 0.012$; [Figure 4](#)).

Sequential changes in the HTLV-1 PVL in HTLV-1-seroconverted pregnant mothers

Among the nine HTLV-1-seroconverted pregnant mothers, there was only one mother (No. 2 in the [Supplementary material S2](#)) for whom the HTLV-1 PVL had been measured more than twice after HTLV-1 seroconversion. Her HTLV-1 PVL increased from 1.09 at her second delivery to 3.90 at her third delivery, which suggests that, even in

HTLV-1-seroconverted pregnant mothers, the HTLV-1 PVL increased over time.

Pregnancy outcomes

Table 2 summarizes the pregnancy outcomes of mothers of known HTLV-1-positive status and mothers that seroconverted to HTLV-1 between pregnancies. There was no statistically significant difference between the two groups in the frequency of any complications that occurred during pregnancy, the length of delivery time, or the sex distribution or birth weight of the babies.

Discussion

This is the first report on the HTLV-1-positive and -seroconversion status of pregnant mothers that participated in APP Nagasaki, and the first to report HTLV-1 PVL chronological data. Our main findings were that: (1) the proportion of those who underwent seroconversion from anti-HTLV-1 antibody negative to positive among pregnant mothers was 0.054%, with a seroconversion incidence rate of 17.5 per 100,000 person-years during the period 2011–2018, (2) HTLV-1 infection had no

adverse effect on pregnancy outcomes in either the HTLV-1-infected or HTLV-1-seroconverted mothers; however, (3) the HTLV-1 PVL increased with increased parity number, and this showed a statistically significant positive correlation in both the HTLV-1-infected and the HTLV-1-seroconverted pregnant mothers.

The estimated incidence rate (17.5 per 100,000 person-years) of HTLV-1 seroconversion among pregnant mothers aged 17–41 years in this analysis was higher than that for female blood donors aged 16–49 years (2.03–8.54 per 100,000 person-years) in Kyushu-Okinawa, where HTLV-1 is endemic (Satake et al., 2016), despite the similar age range of these groups. A possible explanation for this difference might be the eligibility criteria for blood donation, because pregnant women or recently postpartum mothers are not eligible to donate blood in Japan. Instead, the estimated crude incidence rate in this analysis was close to the HTLV-1 seroconversion rate in female repeated blood donors aged over 50 years in Kyushu-Okinawa (11.8–17.0 per 100,000 person-years; Satake et al., 2016). One possible explanation for the HTLV-1 seroconversion rate similarity in these two groups might be related to unprotected sexual contact with HTLV-1-infected partners—the majority of pregnant mothers in our study did not know the HTLV-1 infection status of their partner.

Regarding the PVL in HTLV-1-positive pregnant mothers, we previously reported that the PVL was the highest during the postpartum period (i.e., the period just after delivery) as compared with that during pregnancy terms (i.e., the first, second, and third trimesters; Fuchi et al., 2018). The present study supported the previous report by performing time-sequential analyses of the individual PVL of both HTLV-1-positive and HTLV-1-seroconverted pregnant mothers. In other words, we hypothesize that the positive correlation between the number of deliveries and HTLV-1 PVL found in this study indicates that the elevated HTLV-1 PVL that occurs during the first postpartum period is maintained and then the HTLV-1 PVL increases further during the second postpartum period. Thus, the individual HTLV-1 PVL increased with increased parity number among multiparous women (Figure 4). Alternatively, this finding could suggest that these women are continuously exposed to HTLV-1 from their HTLV-1-positive partners (Stuver et al., 1993; Sullivan et al., 1993; Kaplan et al., 1996). Therefore, they require regular medical check-ups and monitoring of the HTLV-1 PVL for the early detection of HTLV-1-associated diseases, not only by obstetric gynecologists, but also by hematologists. This is primarily because it has been well-established that the higher the PVL in HTLV-1-infected asymptomatic carriers, the higher their risk of developing HTLV-1-associated diseases (Nagai et al., 1998; Iwanaga et al., 2010), but also because a number of case reports have indicated the development of ATL in HTLV-1-positive pregnant mothers with a high PVL (Ohba et al., 1988; Utsumi et al., 1996; Safdar et al., 2002; Amor et al., 2013; Motedayen Aval et al., 2020; Ramassamy et al., 2020). In APP Nagasaki, one asymptomatic HTLV-1-positive pregnant woman developed ATL (Fuchi et al., 2016).

TABLE 2 Pregnancy outcomes in mothers with known HTLV-1-positive status and mothers with HTLV-1 seroconversion during pregnancy.

Characteristic	Mothers HTLV-1-positive at first pregnancy (n = 133)	Mothers seroconverted to HTLV-1-positive (n = 9)	p-Value
No. of deliveries	265	10	–
Complications during pregnancy, n (%)			
No	222 (83.8%)	9 (90.0%)	0.67
Yes	43 (16.2%)	1 (10.0%)	
Length of delivery time, n (%)			
<34 weeks of gestation	222 (83.8%)	9 (90.0%)	0.37
34–36 weeks of gestation	11 (4.2%)	1 (10.0%)	
After 36 weeks of gestation	32 (12.1%)	0	
Sex of child, n (%)			
Unknown	7 (2.6%)	0	0.25
Male	130 (49.1%)	7 (70%)	
Female	128 (48.3%)	3 (30%)	
Birth weight, n (%)			
LFD	18 (6.8%)	1 (10.0%)	0.51
AFD	217 (81.9%)	9 (90.0%)	
HFD	30 (11.3%)	0	

LFD, light for dates; AFD, appropriate for dates; HFD, heavy for dates.

We also report here, for the first time, that even in a HTLV-1-seroconverted mother, the PVL increased between her second and third pregnancies with her increase in age (the second case in [Supplementary material S2](#)). This finding supports the idea that the HTLV-1 PVL increases with parity (or age) even in HTLV-1-seroconverted pregnant mothers. Therefore, we recommend that all HTLV-1-positive women of reproductive age be checked regularly for their HTLV-1 PVL and HTLV-1-associated diseases.

Regarding pregnancy complications in HTLV-1-positive pregnant mothers, previous studies reported no difference in the degree of pregnancy complications between those who were positive and those who were negative for anti-HTLV-1 antibody ([Kusuhara et al., 1987](#); [Rosadas et al., 2019](#)). In the present study, among the 10 deliveries from nine HTLV-1-seroconverted pregnant mothers, only one baby (10% of all deliveries) was born prematurely at 29 weeks of gestation. Although only one premature case occurred, and therefore the sample size was small, the proportion (10%) was greater than the national average for premature cases (5.6%–5.7%) in Japan during 2015–2018 ([Vital Statistics of Japan, 2015–2018](#)). Further large-scale analyses are required to determine whether the occurrence of preterm/premature birth/delivery/labor is higher in HTLV-1-infected and/or HTLV-1-seroconverted pregnant mothers than in uninfected individuals.

Regarding the babies born from HTLV-1-positive mothers, Kusuhara et al. reported that such babies may acquire their own anti-HTLV-1 antibodies by the age of 3 years and continue to acquire such antibodies until the age of 18 ([Kusuhara et al., 1987](#)). Therefore, the obstetric gynecologists participating in APP Nagasaki advised each of the HTLV-1-positive mothers to have their children tested for HTLV-1 antibodies when they reach 3 years of age. In APP Nagasaki, 10 children were born from HTLV-1-seroconverted mothers; of these, one baby girl was given artificial nutrition and tested HTLV-1-negative, while no information was available on the other nine babies.

The major limitation of this study is that the findings were based on a single area of Nagasaki Prefecture; therefore, the results may not apply to other regions of Japan. Another limitation is that our analyses were based only on healthy pregnant women; as such, information on pregnant mothers with possible HTLV-1-associated diseases was lacking. Furthermore, our method was not capable of identifying cases in which a pregnant mother is HTLV-1-negative at the screening date but seroconverts to positive after the screening date. Therefore, our results might be an underestimation. Furthermore, we have little information on the HTLV-1-infection status of the partners of the pregnant mothers. Taking these limitations into account, the actual number of pregnant mothers horizontally infected with HTLV-1 might be higher than what we observed in this study. Also, since our APP project is a kind of a public-health project to avoid mother-to-child HTLV-1-transmission rather than a research-oriented project, the accuracy of data collection may not be perfect and only peripheral blood test and HTLV-1 PVL are regularly

measured. Therefore, even if we are willing to perform a multivariate analysis, it is possible to include only factors such as age and the number of deliveries. However, since aging and the number of deliveries are almost proportional, therefore it is difficult to perform a multivariate analysis as another limitation of our study.

In conclusion, this is the first report on the individual change in HTLV-1 PVL of HTLV-1-positive and HTLV-1-seroconverted pregnant mothers and the infection status of their babies in APP Nagasaki. Although there were no serious adverse effects in the HTLV-1-infected pregnant mothers and their babies, we found that the HTLV-1 PVL of the mothers increased with parity (or age), which suggests that HTLV-1-infected women of reproductive age are continuously exposed to HTLV-1 horizontally from their HTLV-1-infected partners. Therefore, further careful follow-up is needed for both HTLV-1-positive pregnant mothers and their babies.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NK and NF analyzed the data of HTLV-1 test among pregnant women. MI and KM organized the study protocol. NK, MI, and KM wrote the manuscript. YH, SM, NE, and KM collected the data of HTLV-1 tests among pregnant women. HM collected the data regarding Mother to Child transmission of HTLV-1. KY and KM performed the HTLV-1 screening test of pregnant women in Nagasaki. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmicb.2022.1036955/full#supplementary-material>

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Review

How Can We Prevent Mother-to-Child Transmission of HTLV-1?

Kazuo Itabashi ^{1,*}, Tokuo Miyazawa ² and Kaoru Uchimar ^{3,4}

¹ Aiseikai-Memorial Ibaraki Welfare and Medical Center, Ibaraki 3100836, Japan

² Department of Pediatrics, Showa University School of Medicine, Tokyo 1428666, Japan

³ Department of Hematology/Oncology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo 1088639, Japan

⁴ Laboratory of Tumor Cell Biology, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo 1088639, Japan

* Correspondence: kitab@med.showa-u.ac.jp; Tel.: +81-29-353-7171

Abstract: The perception of human T-cell leukemia virus type 1 (HTLV-1) infection as a “silent disease” has recently given way to concern that its presence may be having a variety of effects. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Most patients develop ATL as a result of HTLV-1 mother-to-child transmission. The primary route of mother-to-child transmission is through the mother’s milk. In the absence of effective drug therapy, total artificial nutrition such as exclusive formula feeding is a reliable means of preventing mother-to-child transmission after birth, except for a small percentage of prenatal infections. A recent study found that the rate of mother-to-child transmission with short-term breastfeeding (within 90 days) did not exceed that of total artificial nutrition. Because these preventive measures are in exchange for the benefits of breastfeeding, clinical applications of antiretroviral drugs and immunotherapy with vaccines and neutralizing antibodies are urgently needed.

Keywords: human T-cell leukemia virus type 1 (HTLV-1); adult T-cell leukemia (ATL); mother-to-child transmission; antenatal screening; prevention; nutritional regimens



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1. Introduction

There are seven known carcinogenic viruses: Epstein–Barr virus (EBV; also known as human herpesvirus 4 (HHV4)), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell leukemia/lymphotropic virus type 1 (HTLV-1), human papilloma virus (HPV), Kaposi’s sarcoma herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)), and Merkel cell polyomavirus (MCV). These viruses are responsible for approximately 15% of all human cancers [1]. Among these viruses, HTLV-1 was the first retrovirus discovered to be carcinogenic [2,3], and the patients showed unique clinical characteristics. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [4,5]. HTLV-1 carriers have an estimated lifetime risk of 2–5% for the development of ATL [6] and 0.25–1.8% for HAM/TSP [7,8]. Both diseases exhibit serious clinical manifestations and poor prognosis despite therapeutic efforts. In addition to these two diseases, HTLV-1-associated uveitis is widely known [9]. Although ATL and HAM/TSP have been recognized as major outcomes of HTLV-1 infection, they account for less than 10% of the infected population. A recent meta-analysis showed that disease outcomes (morbidity and mortality) for which HTLV-1 is not a necessary diagnostic criterion are clearly associated with HTLV-1 infection (10). This analysis showed a 57% increased risk of early mortality, independent of ATL or HAM/TSP. As ATL and HAM/TSP are present in less than 10% of cases, increased mortality cannot be explained by these two diseases alone [10]. Thus, HTLV-1 infection is likely to affect human health in more ways than currently known and is a global burden [11,12].