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Cerebrospinal Fluid Lactate and Pyruvate Concentrations and Their Ratio in Children: Age-related Reference Intervals

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Background: **Lactate (L) and pyruvate (P) concentrations in cerebrospinal fluid (CSF) and the L/P ratio have diagnostic value in numerous primary and acquired disorders affecting the central nervous system, but age-related reference values are not available for children.**

Methods: **We analyzed CSF and blood lactate and pyruvate concentrations and their ratio in a 4-year retrospective survey of a children's hospital laboratory database. Reference intervals (10th–90th percentiles) were established from data on 197 hospitalized children. A recent regression modeling method was used to normalize and smooth values against age. The model equation of best fit was calculated for each variable.**

Results: **Slight age-related variations were shown by the model, with an increase in lactate, a decrease in pyruvate, and a resulting increase in the L/P ratio with increasing age. However, the SD did not vary with age. We defined the upper limit of the reference intervals as the 90th percentiles, which from birth to 186 months of age varied continuously from 1.78 to 1.88 mmol/L (6%), 148 to 139 μmol/L (6%), and 16.9 to 19.2 (14%) for lactate, pyruvate, and the L/P ratio, respectively. At a threshold of 2 (in *Z*-score units), the sensitivity for a subgroup of inborn errors of metabolism (respiratory chain disorders) was 73%, 42%, and 31% for lactate, pyruvate, and the L/P ratio, respectively.**

Conclusions: **In children, CSF lactate and pyruvate concentrations and their ratio appear to vary slightly with age. Average 90th percentile values of 1.8 mmol/L, 147 μmol/L, and 17, respectively, could be used in infants up to 24 months of age. In older children, age-adjusted reference intervals should be used, especially when values are close to the 90th percentile.**

Cytosolic lactate and pyruvate concentrations depend on the activity of tightly regulated anabolic and catabolic pathways, which are most active in liver, kidney, muscle, and the central nervous system. Regarding the reaction catalyzed by lactate dehydrogenase (EC 1.1.1.27), the ratios of lactate to pyruvate (L/P)[4] and NADH to NAD^+ are strictly interdependent through their equilibrium constant, K'_{eq}. Thus, the L/P ratio is classically considered as a marker of cytosolic redox status ($NADH/NAD^+$) *(1)*.

Several acquired disorders, such as bacterial meningitis *(2)*, cerebral hypoxia *(3)*, and status epilepticus *(4)*, can increase the cerebrospinal fluid (CSF) lactate concentration. Lactate concentrations in CSF have also been reported to be increased in individuals with several inborn errors of metabolism (IEM) that can affect the central nervous system, such as pyruvate dehydrogenase (PDH) deficiency *(5)*, and respiratory chain (RC) disorders *(6)*. In these primary enzyme defects, simultaneous determination of lactate and pyruvate in CSF is a valuable tool for differential diagnosis of suspected PDH deficiency. To our knowledge, only one published study has given the usual range of both lactate and pyruvate in CSF, but it was based on adult cisternal puncture samples *(7)*. Only CSF lactate ranges have been established in children, in small cohorts *(2, 4, 8, 9)*.

The main purpose of this study was to determine the distribution of CSF lactate and pyruvate concentrations and their ratio in children, together with their age-depen-

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[4] Nonstandard abbreviations: L/P, lactate/pyruvate; CSF, cerebrospinal fluid; IEM, inborn errors of metabolism; PDH, pyruvate dehydrogenase; and RC, respiratory chain.

dent reference intervals. We conducted a retrospective survey of CSF analytical data on patients admitted to our children's hospital with suspected IEM or neurologic disorders over a 4-year period. Many pediatric reference ranges have been shown to change with age, but despite efforts by several authors *(10, 11)*, arbitrary methods are still being used to estimate age-specific reference intervals. Moreover, when the mean is modeled as being age-related, the age dependency of the SD is often not investigated. Here, we used the method of Royston and Wright *(12)*, which is based on regression modeling of both the mean and the SD across age. The diagnostic values of the reference intervals thus defined were tested in a group of patients with IEM (RC disorders or PDH deficiency). Finally, CSF values were compared with values determined in paired blood samples.

Patients and Methods

PATIENTS

For obvious ethical reasons, CSF could not be sampled in healthy children. We therefore used data for CSF specimens collected from children hospitalized in our pediatric institution between January 1997 and March 2002 for neurologic investigations and/or suspected metabolic diseases. Patients were included in this survey if they underwent assays for lactate and pyruvate in CSF and had whole blood drawn simultaneously in the fed state (after breakfast). CSF specimens were excluded in any of the following circumstances: clinical signs of meningitis, cerebral hypoxia, or status epilepticus; positive culture; positive Gram staining; bloody aspect; or xanthochromic supernatant with an erythrocyte-containing centrifuge pellet. If a patient was retested during the study period, only the first measurements were included.

The 253 patients meeting these criteria were divided into three groups:

- The reference group (n = 197) included all patients who had no metabolic abnormalities and who had blood lactate concentrations within our in-house age-related reference interval *(13)*.
- The hyperlactatemic group (n = 16) comprised patients in whom no metabolic abnormalities were found but whose blood lactate was increased.
- The IEM group (n = 30) comprised children with RC disorders (n = 26) or PDH deficiency (n = 4) diagnosed on clinical, biochemical, and/or genetic grounds. Among the 26 patients classified in the RC disorder subgroup, 23 had specific clinical presentations (i.e., Alpers or Leigh syndromes, nonobstructive cardiomyopathy), a typical histopathologic aspect on muscle and liver biopsy (i.e., ragged red fibers, lipid accumulation), mitochondrial DNA defects and (*a*) severe single enzyme activity deficiencies (n = 15), (*b*) severe multiple enzyme activity deficiencies in both muscle and liver (n = 1), (*c*) moderate single enzyme activity deficiencies in both muscle and liver (n = 4), or (*d*) no clear enzyme activity deficiency (n = 3). The last three patients had Menkes disease and a secondary RC disorder attributable to impairment of copper-dependent cytochrome *c* oxidase. Ten children with other forms of IEM (e.g., enzymatic β-oxidation deficiencies, sulfite oxidase deficiency, and Krabbe disease) were excluded.

SPECIMEN COLLECTION

Blood was drawn from an indwelling catheter in an arm vein (kept open by saline infusion) with no tourniquet and avoiding hand exercise. Samples were deproteinized immediately at the bedside by adding two volumes of ice-cold 1 mol/L perchloric acid. After thorough mixing, samples were stored at −20 °C for no more than 7 days and were thawed immediately before analysis.

CSF was obtained by lumbar puncture in strict aseptic conditions and was immediately stored at −20 °C for no more than 7 days. Samples were deproteinized as above after thawing and immediately before use.

ASSAYS

Lactate was assayed in blood and CSF with a KonePro apparatus and lactate oxidase methodology (Roche Diagnostics). The between-run imprecision (CV; n = 63) for two control sera was 1.3% (1.59 mmol/L) and 1.1% (4.33 mmol/L), respectively. The between-run imprecision (n = 20) for two CSF controls was 0.7% at both 1.92 and 6.97 mmol/L.

Pyruvate was assayed in blood and CSF with a KonePro apparatus and lactate dehydrogenase methodology (Sigma-Aldrich). After deproteinization, the supernatants were neutralized by adding one sample volume of 1.1 mol/L K_3PO_4. The between-run imprecision (CV; n = 15) for two control sera was 2.9% (89 μmol/L) and 2.4% (161.7 μmol/L), respectively. The between-run imprecision (n = 15) for two CSF controls was 3.8% (130.8 μmol/L) and 3.2% (287.3 μmol/L), respectively.

STATISTICAL ANALYSIS

Quantitative variables are shown as medians (range) and qualitative variables as frequencies (percentages). The relationship between blood and CSF lactate concentrations was tested using the Spearman nonparametric correlation coefficient.

Age-specific reference intervals for CSF values were estimated by the simplified parametric method described by Wright and Royston *(14)*. A reference interval is the range of values encompassed by a pair of symmetrically placed extreme percentiles, such as the 5th and 95th for a 90% interval. Values that lie outside the reference limits are regarded as unusual or extreme and may indicate the presence of a disorder such as IEM. Assuming a gaussian distribution of the variable at each age, a percentile is calculated by using the well-known formula: percentile = mean + $K \times$ SD, where the mean and SD are defined for a given age and K is the corresponding percentile constant of the standard gaussian distribution (for example, for the

10th and 90th percentiles curves, $K = \pm 1.28$). The aim is to find functions that adequately represent how the mean and SD change with age.

Initial natural logarithmic transformation is applied if required to reduce the positive skewness and heteroscedasticity of measurements of interest. A suitable function for the mean is then determined as a polynomial of degree *m* fitted by least-squares regression of the measurement of interest on age. The gender variable was entered in the model to determine whether a significant improvement occurred in the model likelihood. The fitted values from the regression give the estimated mean curve and the scale absolute residuals (difference between the measurements and the estimated curve for the mean with the sign removed and multiplied by $\sqrt{\pi/2}$). If the scale absolute residuals appear to show no trend with age, the SD is estimated as the SD of the residual of the measurement of interest from the regression on age. The model fit is assessed by calculating the SD scores (Z-score) as Z = (measurement − mean)/SD and expressed in SE. The ordered Z-scores are plotted to provide a graphic check of normality, and the Shapiro–Francia *W′* test is used as a formal test of nonnormality. If normality is accepted, no further modeling is required. Percentile estimated and reference intervals are calculated by substituting the fitted curves of the mean and SD into the equation of percentile. When the variable being modeled is log-transformed, percentiles curves on the original scale are obtained by applying antilogs to the calculated curves. Statistical analysis was performed using the SAS 8.02 software package for PC (SAS Inc.).

Results

REFERENCE GROUP

The reference population (n = 197) was composed of 83 girls and 114 boys (Fig. 1, A–C). The main descriptive statistics derived from lactate and pyruvate concentrations and the L/P ratio in CSF and blood are reported in Table 1. Fig. 1 shows scatter plots of CSF values against age and sex. To be modeled, pyruvate concentrations and the L/P ratio required natural logarithmic scale transformation. No influence of gender was found, and there was no evidence of age dependency in the scale absolute residuals calculated for the three variables; the SD was therefore estimated as a constant. The three model equations were:

CSF lactate (mmol/L):

$$\text{Mean} = 1.452 + 0.00055 \times \text{age} \quad (\text{SD} = 0.255) \qquad (1)$$

CSF pyruvate (μmol/L):

$$\text{Mean} = e^{(4.72 - 0.00034 \times \text{age})} \quad (\text{SD} = 0.218) \qquad (2)$$

CSF L/P ratio:

$$\text{Mean} = e^{(2.55 + 0.00071 \times \text{age})} \quad (\text{SD} = 0.217) \qquad (3)$$

where age is in months, lactate and pyruvate are in mmol/L in Eq. 3, and $e = 2.71828$.

The curves of the mean plus the 80% central reference intervals (10th and 90th percentile) obtained with the above models are shown in Fig. 1. As a consequence of logarithmic transformation, the 90th percentile curves for pyruvate and the L/P ratio were obtained by applying antilogs to the corresponding formula (mean + 1.28 SD). For example, the three model equations giving the 90th percentiles for a 14-month-old child were:

CSF lactate:

$$C_{90\text{th}} = (1.452 + 0.00055 \times 14) + (1.28 \times 0.255)$$

$$= 1.79 \text{ mmol/L}$$

CSF pyruvate:

$$C_{90\text{th}} = e^{[4.72 - (0.00036 \times 14) + (1.28 \times 0.218)]} = 148 \text{ mmol/L}$$

CSF L/P ratio:

$$C_{90\text{th}} = e^{[2.55 + (0.00071 \times 14) + (1.28 \times 0.217)]} = 17$$

We found a correlation between CSF and blood concentrations of lactate and pyruvate (CSF, $r = 0.34$; $P < 0.001$; blood, $r = 0.74$; $P < 0.001$) and between the lactate concentration and the L/P ratio (CSF, $r = 0.40$; $P < 0.001$; blood, $r = 0.53$; $P < 0.001$).

We also found a correlation for lactate values between CSF and paired blood samples ($r = 0.25$; $P = 0.0004$) and for the L/P ratio ($r = 0.31$; $P < 0.0001$), but not for pyruvate concentrations ($r = 0.13$; $P = 0.08$).

HYPERLACTATEMIC GROUP

This group comprised 16 children (4 girls and 12 boys; ages, 1 month to 14 years) with hyperlactatemia (1.8–4.8 mmol/L; Fig. 1, D–F). Ten (62.5%) of these patients had CSF lactate values above the 90th percentile, but we found no correlation between CSF and blood lactate values.

IEM GROUP

This group comprised 30 children with either RC disorders or PDH deficiency (Fig. 2).

RC disorder subgroup. This group comprised 11 girls and 15 boys (ages, 1.3 months to 16.3 years). CSF lactate concentrations were above the 90th percentile in 20 of the 26 patients with RC disease. Fourteen of these 20 patients also had increased blood lactate values, whereas the remaining 6 children had blood lactate values within our age-related reference values. The six children with CSF concentrations within the reference interval also had blood concentrations within reference values. Three of them had no clear enzyme activity deficiency, two had moderate complex IV deficiencies in both muscle and liver, and the last had severe encephalomyopathy with complete complex I deficiency. Their CSF and blood L/P

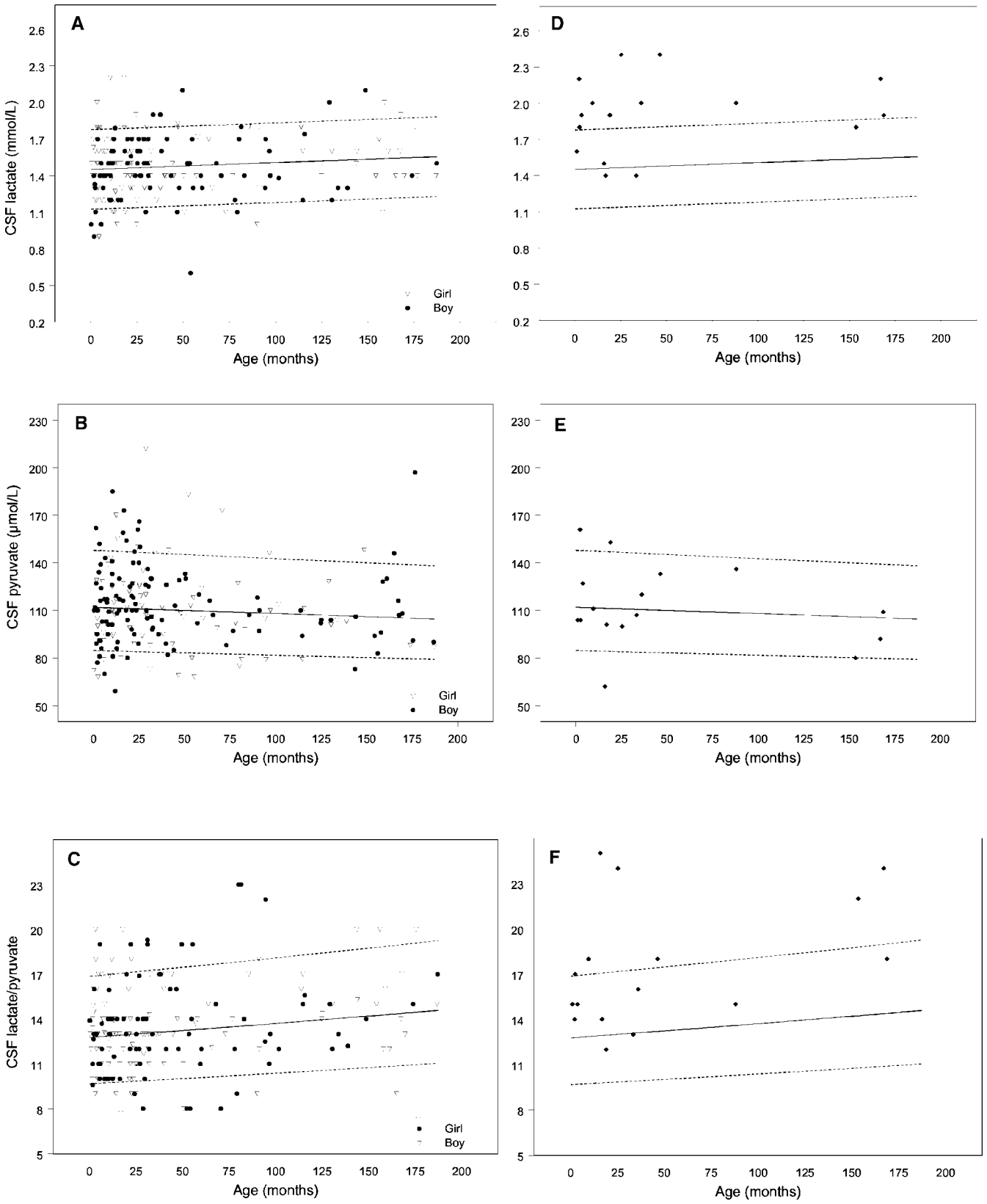

Fig. 1. Scatter plots of the reference (*A*, *B*, and *C*) and hyperlactatemic group values (*D*, *E*, and *F*) vs age with the 10th and 90th percentiles (*dotted lines*) and means (*solid lines*) calculated for CSF lactate (*A* and *D*), pyruvate (*B* and *E*), and L/P ratio (*C* and *F*).

●, boys; ▽, girls. L/P ratio is given in mmol/mmol.

Table 1. Descriptive statistics in CSF and blood in the reference group.

	Age, months	Lactate, mmol/L		Pyruvate, μmol/L		L/P ratio, mmol/mmol	
		CSF	Blood	CSF	Blood	CSF	Blood
Boys (n = 114)							
Median	22.8	1.5	1.3	110	124	13	11
Range	0.3–187	0.9–2.2	0.5–2.2	59–197	59–217	7–23	7–22
Girls (n = 83)							
Median	28.9	1.4	1.4	109	122	13	11
Range	0.2–187	0.6–2.1	0.5–2.2	68–212	50–203	8–23	6–26
Total (n = 197)							
Median	25.6	1.5	1.3	110	124	13	11
Range	0.2–187	0.6–2.2	0.5–2.2	59–212	50–217	7–23	6–26

ratios were within the reference values, except for the last patient, who had an increased CSF L/P ratio of 23.

CSF pyruvate concentrations were above the 90th percentile in 16 of the 26 patients, and CSF lactate was always increased in these 16 patients. Nine of these 16 patients also had increased blood pyruvate values, whereas the other 7 had values within our reference interval. As was observed for lactate, paired blood pyruvate concentrations were always within reference values when the CSF concentration was within reference values (n = 10).

The CSF L/P ratio was above the 90th percentile in 15 of the 26 patients. Thirteen of these 15 patients had increased CSF lactate concentrations, whereas the other 2 had values within the reference interval.

PDH deficiency subgroup. This group comprised 1 girl and 3 boys (ages, 21.5 months to 9.4 years). CSF lactate and pyruvate concentrations showed a proportional increase in all four children, yielding a normal (three cases) or slightly increased L/P ratio (92nd percentile). Similar trends were seen in blood values (not shown), with an increased (three cases) or subnormal lactate concentration, a consistently increased pyruvate concentration, and a consistently normal L/P ratio.

Because the reference values varied with age, their distributions were plotted as *Z*-scores. As illustrated in Fig. 3, CSF values in the RC disorder subgroup differed significantly from values in the reference group, in which, by definition, the median was 0 and the lower and upper quartiles were −1 and +1, respectively. We then calculated the sensitivity and specificity of CSF lactate and pyruvate concentrations and their ratio for the studied metabolic disorders, using a *Z*-score cutoff of >2 SE, by analogy to the 97.5th percentile of the gaussian distribution (Table 2).

Discussion

The main purpose of this study was to determine age-related reference intervals of CSF lactate and pyruvate and their ratio in children. The choice of method used to estimate age-specific reference intervals is crucial because inaccurate percentiles may mislead physicians as to a child's true metabolic state and increase the risk of suboptimal clinical care. It is still common to see reports of percentile estimates that vary in a jagged fashion with age, usually because the authors calculated the means and SDs with no attempt at smoothing. In this study we used least-squares regression analysis to estimate both the mean and SD curves as polynomial functions of age. Because the scale absolute residuals showed no trend with age, the SD was considered to be age-independent. The normality of the distribution was assessed by plotting the ordered *Z*-scores against age. The calculated curves expressing the mean of each variable were straight lines ($a + b \times$ age), the best fits for pyruvate values and L/P ratios being obtained after natural logarithmic transformation. Consequently, their mean and percentile curves on the original scale were obtained by applying antilogs to the calculated curves.

Regarding the values for the reference group, the three model equations suggested a slight but continuous variation of CSF lactate and pyruvate concentrations with age in children up to 186 months (15.5 years). Because the lactate concentration increased whereas that of pyruvate decreased, the L/P ratio also increased. Given the size of our sample, we defined the limits of the reference intervals between the 10th and 90th percentiles, but in clinical practice, only the upper 90th percentile limit is of interest. On the basis of this upper limit, the CSF 90th percentiles between birth and 186 months would vary between 1.78 and 1.88 mmol/L, 148 and 139 μmol/L, and 16.9 and 19.2 for lactate, pyruvate, and the L/P ratio, respectively. These variations with age appear relatively small: they represent, respectively 6%, 6%, and 14% of the values observed at birth. Taking into account the CVs of the CSF lactate and pyruvate assays, minor variations might be considered insignificant. Thus, in clinical practice we propose as a threshold the 90th percentile values observed for infants up to 24 months of age, i.e., 1.8 mmol/L, 147 μmol/L, and 17 for lactate, pyruvate, and the L/P ratio, respectively. This age range, from birth to 24 months, is critical for the detection of many inborn and acquired pathologies and corresponds to the most strongly represented age group in our reference population. The de-

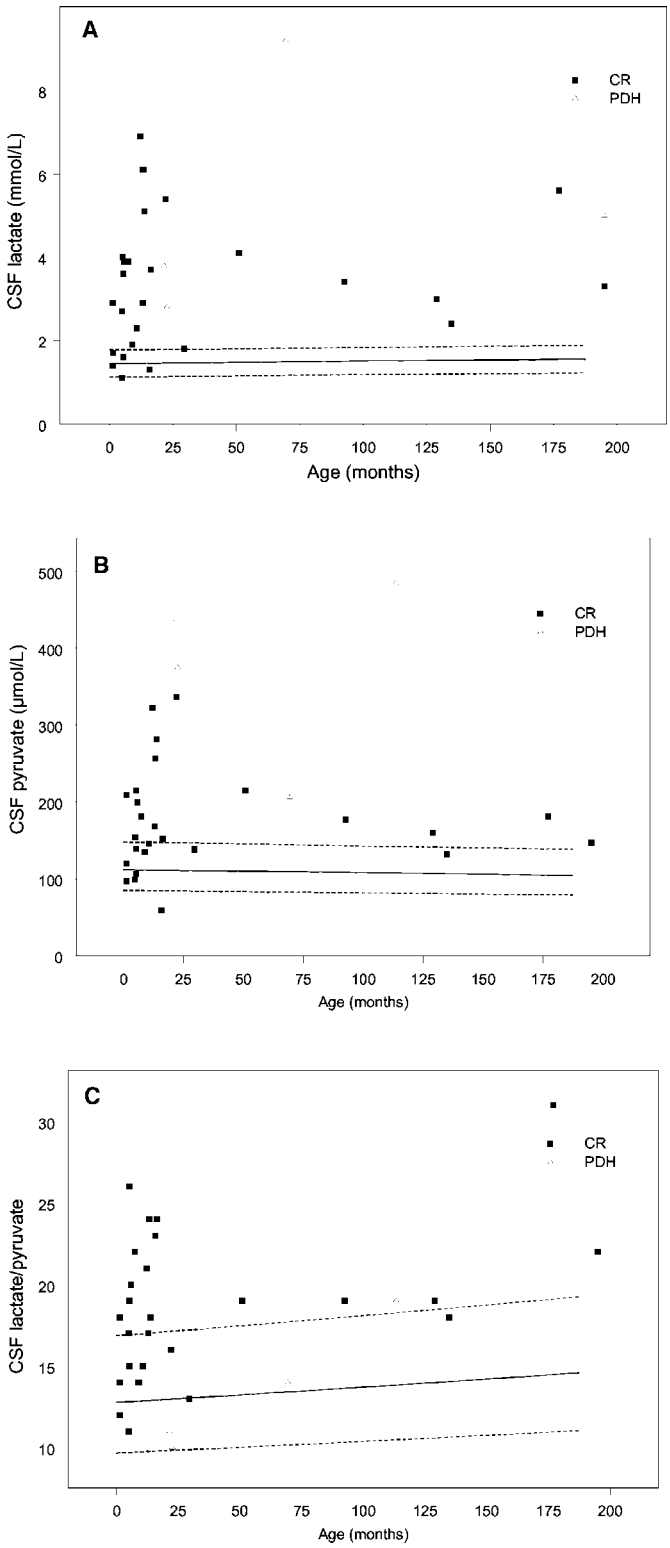

Fig. 2. Scatter plots of the IEM group values vs age.

(*A*), CSF lactate; (*B*), CSF pyruvate; (*C*), CSF L/P (mmol/mmol). ■, RC diseases; △, PDH deficiency.

rived equations should be used for children beyond 24 months of age.

The positive correlation between lactate and pyruvate concentrations and between lactate concentrations and the L/P ratio in both CSF and blood highlight their interdependency through the equilibrium constant K'_{eq} and through the biological variability of the NADH/NAD^+ ratio. Blood lactate concentrations have been reported to decrease with age *(13, 15)*; they appear to show opposite trends in CSF and blood in childhood. However, this age dependency of lactate concentrations was not found by Hutchesson et al. *(9)* in 39 healthy children 0.03–17.7 years of age (median, 1.39 years), although the upper limit of their CSF lactate values (1.97 mmol/L, mean + 2 SD) was close to that observed here. Perhaps because of the small size of the study population, the latter authors saw no significant difference in either CSF or plasma lactate concentrations between the upper and lower halves of the age distribution. Nevertheless, for a given age, the same authors found a positive correlation ($r = 0.38$; $P < 0.05$) between lactate concentrations in CSF and plasma, which is in keeping with the positive correlation we found between CSF and blood for both lactate concentrations ($r = 0.25$; $P = 0.0004$) and the L/P ratio ($r = 0.31$; $P < 0.0001$). This correlation retrospectively justifies our choice of hyperlactatemia as an exclusion criterion for the reference group but is difficult to explain in the light of current knowledge on physiologic lactate exchanges between CSF and blood.

Indeed, lactate concentrations in CSF result from a complex balance between efflux and influx through the blood–brain barrier and through the plasma membrane of central nervous system cells. It has been reported *(16)* that blood and CSF lactate equilibrates slowly because of the apparently low rate of permeation from brain tissue to venous blood and the low rate of lactate extraction from the circulation. The p*K* of lactic acid (3.86) ensures that it dissociates almost entirely to the lactate anion at physiologic pH. This charged species cannot cross the various plasma membranes by free diffusion, but requires a specific transport mechanism provided by proton-linked monocarboxylate transporters *(17)*. Although these transporters catalyze the facilitated diffusion of most lactate, they are also essential for the transport of other monocarboxylates, such as pyruvate. On this basis, and in agreement with several other reports *(18, 19)*, it was assumed that lactate concentrations in CSF could show short-term variations independent of blood variations. Thus, in acute disorders, because brain tissue is extremely dependent on aerobic glucose metabolism, CSF lactate should be a better indicator of local metabolism than is blood lactate.

CSF lactate concentrations were more sensitive for RC disorders than were blood lactate concentrations (not shown). This is not surprising because suspected neurologic disorders were criteria for inclusion in the IEM study group. It is noteworthy that blood lactate concentrations were always within our reference values when CSF lactate was normal (not shown). However, six children (23%) had no increase in lactate in either CSF or

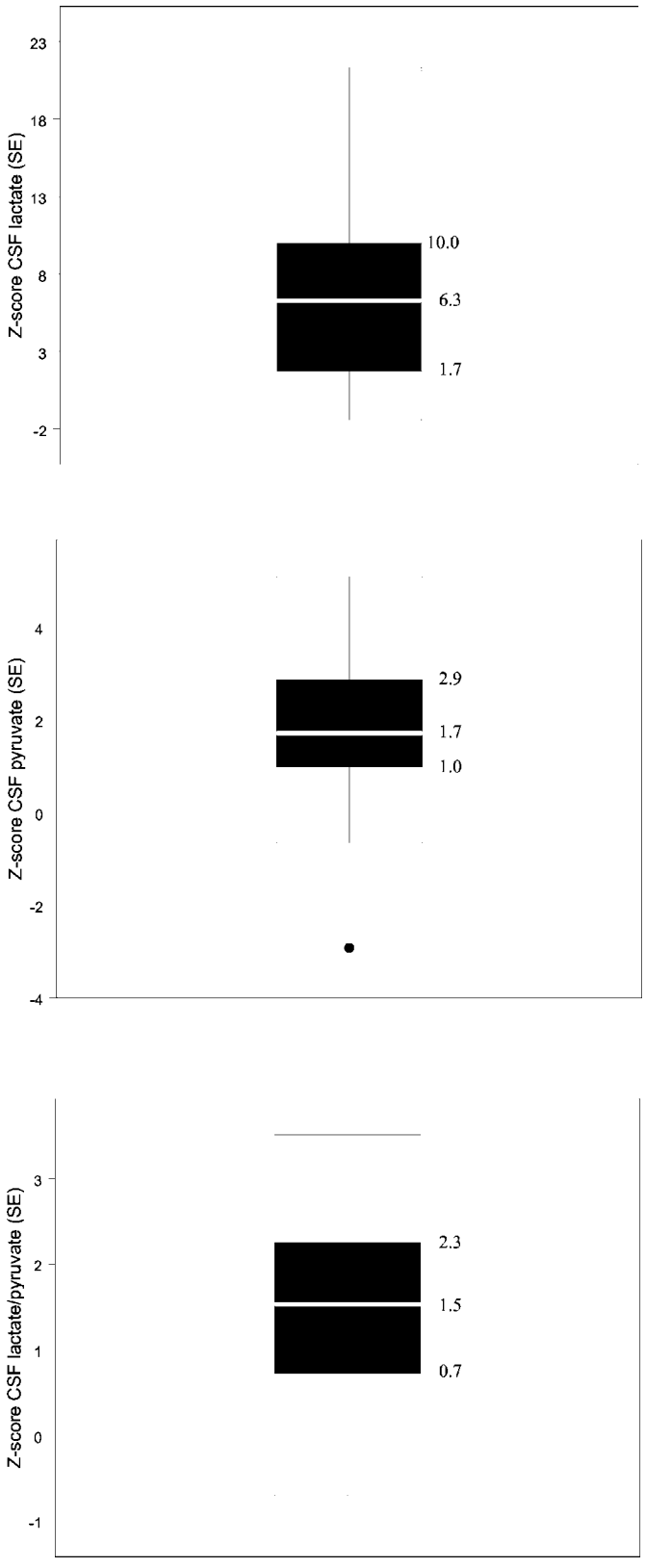

Fig. 3. Box-plots of the *Z*-score values of CSF lactate (*top*), pyruvate (*middle*), and L/P ratios (*bottom*) calculated for the RC disorder subgroup.

The *box* indicates the lower and upper quartiles, and the *central line* is the median. The *ends* of the *whiskers* are the 2.5 and 97.5 values. ●, outlier.

Table 2. Diagnostic values calculated using Z-scores >2 SE and applied to the RC disorder subgroup.

	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Lactate	73	97	79	96
Pyruvate	42	97	65	93
L/P ratio	31	97	62	91
Lactate and pyruvate	73	95	66	96

blood. This might reflect mitochondrial heteroplasmy or tissue-specific partial enzyme defects.

CSF pyruvate concentrations showed a similar trend in patients with RC disorders, albeit with lower diagnostic sensitivity than CSF lactate. In keeping with the expected increase in the $NADH/NAD^+$ ratio in RC disorders, lactate concentrations in both CSF and blood were always increased when pyruvate was increased. Simultaneous determination of lactate and pyruvate is used to determine cytosolic redox status (i.e., the L/P ratio) in several forms of IEM, and especially PDH deficiency. Both pyruvate and lactate concentrations are increased in PDH deficiency, but the L/P ratio remains normal or only slightly decreased *(20)* because the mitochondrial RC is not impaired. However, CSF appears to be more clinically relevant for pyruvate determinations because pyruvate concentrations in blood may be highly sensitive to sample preparation *(13)*, giving rise to artificially low values (attributable to lactate dehydrogenase activity) and therefore to falsely high L/P ratios.

In conclusion, this work highlights the smooth variations of CSF lactate and pyruvate concentrations and their ratio during childhood. The regression modeling approach used here could be applied to determining age-related reference intervals of many other analytes in children.

References

1. Medina JM, Tabernero A, Tovar JA, Martin-Barrientos J. Metabolic fuel utilization and pyruvate oxidation during the postnatal period [Review]. J Inherit Metab Dis 1996;19:432–42.
2. Cameron PD, Boyce JM, Ansari BM. Cerebrospinal fluid lactate in meningitis and meningococcaemia. J Infect 1993;26:245–52.
3. Fernandez F, Verdu A, Quero J, Ferreiros MC, Daimiel E, Roche MC, et al. Cerebrospinal fluid lactate levels in term infants with perinatal hypoxia. Pediatr Neurol 1986;2:39–42.
4. Calabrese VP, Gruemer HD, James K, Hranowsky N, DeLorenzo RJ. Cerebrospinal fluid lactate levels and prognosis in status epilepticus. Epilepsia 1991;32:816–21.
5. Matsuda J, Ito M, Naito E, Yokota I, Kuroda Y. DNA diagnosis of pyruvate dehydrogenase deficiency in female patients with congenital lactic acidaemia. J Inherit Metab Dis 1995;18:534–46.
6. Jackson MJ, Schaefer JA, Johnson MA, Morris AA, Turnbull DM, Bindoff LA. Presentation and clinical investigation of mitochondrial respiratory chain disease. A study of 51 patients. Brain 1995; 118:339–57.
7. Vamosi B, Dioszeghy P, Molnar L. Lactate and pyruvate content of the human cisternal cerebrospinal fluid. Normal values, age and

sex dependency, correlations with glucose concentrations. Arch Psychiatr Nervenkr 1983;232:521–32.
8. Knight JA, Dudek SM, Haymond RE. Increased cerebrospinal fluid lactate and early diagnosis of bacterial meningitis [Letter]. Clin Chem 1979;25:809–10.
9. Hutchesson A, Preece MA, Gray G, Green A. Measurement of lactate in cerebrospinal fluid in investigation of inherited metabolic disease. Clin Chem 1997;43:158–61.
10. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. Br J Obstet Gynaecol 1994;101:29–34.
11. Royston P. Constructing time-specific reference ranges. Stat Med 1991;10:675–90.
12. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound Obstet Gynecol 1998;11:30–8.
13. Touati G, Rigal O, Lombes A, Frachon P, Giraud M, Ogier de Baulny H. In vivo functional investigations of lactic acid in patients with respiratory chain disorders. Arch Dis Child 1997;76:16–21.
14. Wright EM, Royston P. Simplified estimation of age-specific reference intervals for skewed data. Stat Med 1997;16:2785–803.
15. Soldin JS, Brugnara C, Gunter KC, Hicks JM, eds. Pediatric reference ranges, 2nd ed. Washington, DC: AACC Press, 1997: 181pp.
16. LaManna JC, Harrington JF, Vendel LM, Abi-Saleh K, Lust WD, Harik SI. Regional blood-brain lactate influx. Brain Res 1993;614: 164–70.
17. Halestrap AP, Price NT. The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation [Review]. Biochem J 1999;343:281–99.
18. Stacpoole PW, Bunch ST, Neiberger RE, Perkins LA, Quisling R, Hutson AD, et al. The importance of cerebrospinal fluid lactate in the evaluation of congenital lactic acidosis. J Pediatr 1999;134: 99–102.
19. Posner JB, Plum F. Independence of blood and cerebrospinal fluid lactate. Arch Neurol 1967;16:492–6.
20. Poggi-Travert F, Martin D, Billette de Villemeur T, Bonnefont JP, Vassault A, Rabier D, et al. Metabolic intermediates in lactic acidosis: compounds, samples and interpretation [Review]. J Inherit Metab Dis 1996;19:478–88.