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No role for CSF myelin basic protein levels in patients treated for childhood acute lymphoblastic leukemia

THÈSE

Préparée sous la direction du Docteur Maja Beck-Popovic, Privat-Docent et Maître d'Enseignement et de Recherche, avec la co-direction du Professeur Sergio Fanconi, et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

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Résumé

Introduction

La prophylaxie du système nerveux central lors d'un diagnostic de leucémie lymphoblastique aiguë de l'enfant a permis de réduire le risque de rechute mais a été associée dans certains cas à des neurotoxicités cliniques ou des anomalies radiologiques. Des moyens de prédire ces neurotoxicités font défaut, en particulier en raison de l'absence de corrélation claire entre les signes cliniques et les images radiologiques. Quelques auteurs ont suggéré que les taux de protéine basique de la myéline (MBP) mesurés dans le liquide céphalo-rachidien pouvaient avoir un intérêt dans ce contexte. Une étude rétrospective de ces taux en relation avec des données cliniques et radiologiques est présentée dans ce travail.

Matériel et Méthodes

Les taux de MBP mesurés dans le liquide céphalo-rachidien lors d'administration de chimiothérapie intrathécale, les examens cliniques neurologiques et les rapports radiologiques ont été rétrospectivement étudiés chez nos patients. Les données concernant des difficultés académiques éventuelles, ainsi que le niveau académique atteint ont été récoltées par l'intermédiaire de contacts téléphoniques réguliers organisés dans le cadre du suivi à long terme de nos patients.

Résultats

Un total de 1248 dosages de MBP chez 83 patients, 381 examens neurologiques chez 34 patients et 69 rapports d'investigations neuroradiologiques chez 27 patients ont été analysés. Cinquante-deux patients ont eut au moins un taux anormal de MBP. Des anomalies radiologiques ont été décrites chez 47% de ces patients, parmi lesquels 14% ont présenté des difficultés scolaires sous une forme ou sous une autre. La proportion de patients ayant présenté des difficultés scolaires dans les groupes avec taux de MBP normal mais sans anomalies radiologiques décrites ou sans investigations radiologiques étaient respectivement de 0% et 3%, inférieurs dans tous les cas au groupe avec des taux normaux de MBP (100%, 22% and 5% respectivement).

Discussion

Tout en prenant en compte les limitations dues à l'aspect rétrospectif de cette étude, nous avons conclu à une utilité limitée de ces dosages systématiques comme indicateur d'une neurotoxicité induite par le traitement dans le contexte de nos patients oncologiques.

No Role for CSF Myelin Basic Protein levels in patients treated for Childhood Acute Lymphoblastic Leukemia

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Abstract

Introduction

Central nervous system (CSF) prophylaxis of childhood acute lymphoblastic leukemia has dropped rates of relapses but has been associated with neurotoxicity and imaging abnormalities. Predictors of neurotoxicity are lacking, because of inconsistency between clinical symptoms and imaging. Some have suggested CSF Myelin Basic Protein (MBP) levels to be of potential interest. A retrospective analysis of MBP levels in correlation with clinical and radiological data is presented.

Materials and Methods

MBP levels obtained at the time of intrathecals, charts, and neuroradiology reports were retrospectively analyzed. Academic achievement data were obtained from phone contacts with patients and families.

Results

We retrieved 1248 dosages of MBP in 83 patients, 381 neurological exams in 34 patients and 69 neuroradiological investigations in 27 patients. Fifty-two patients had abnormal MBP levels. Radiological anomalies were present in 47% of those investigated, 14% of them having school difficulties. Proportions of patients with school difficulties in the groups with abnormal MBP levels but no radiological anomalies or with no radiological investigations were 0% and 3% respectively, which was lower than in the group of patients with normal MBP levels (100%, 22% and 5% respectively).

Discussion

Notwithstanding the retrospective character of our study, we conclude that there is limited usefulness of systematic dosage of MBP as indicator of treatment-induced neurotoxicity in ALL patients.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy. Over the years, progress in risk-specific treatment tailoring treatment intensity to biological risk factors has dramatically improved survival of affected patients, with a cure rate reaching 70-80% nowadays. The introduction of central nervous system (CNS) prophylaxis was a crucial step in the improvement of survival, decreasing the incidence of CNS relapse to less than 5%[1;2]. CNS prophylaxis has evolved over the years from cranio-spinal irradiation to intrathecal and intravenous administration of chemotherapeutic agents such as methotrexate[3-7]. Although very efficacious, both of these methods have been associated with abnormal radiological findings, in particular on MRI, with or without clinical symptoms, leukoencephalopathy (LE) being one of the most severe form [8-10]. Clinical neurotoxicity secondary to CNS prophylaxis, extending from simple seizures to severe and permanent debilitating encephalopathy due to acute demyelization, is well described in the available literature [11-16]. Concerns about long term neurotoxicity in terms of academic achievement and IQ scores have led to trials evaluating the omission of CNS prophylactic radiotherapy in low risk patients[17], the reduction of radiotherapy doses in higher risk patients or the use of different administration methods like hyperfractionation [18]. Inconsistency in correlation between clinical symptoms and imaging explains the persistent lack of tools for early detection of severe alterations.

Myelin basic protein (MBP), a complex of proteins stabilizing the myelin sheet in the central nervous system that can be measured in the cerebrospinal fluid (CSF) [19], has been suggested by some authors to potentially correlate with acute demyelization secondary to MTX[11;20-26]. Little is known, however, about its significance as a predictor of acute or late clinical toxicity, its correlation with radiological images as well as academic achievement [27].

In the laboratory of neurochemistry at our institution, CSF MBP levels have been measured routinely from 1981 to 2001 in most of our ALL patients because of local interest in this protein. In order to evaluate whether this analysis should be continued, we decided to retrospectively review the results in correlation with clinical and

radiological data in order to establish whether CSF MBP levels can be used as a predictor of treatment related CNS toxicity.

Materials and Methods

Clinical charts, neuroradiology reports and CSF MBP levels of patients treated for B-precursor and T-cell ALL at the Pediatric Hematology and Oncology Unit of the University Hospital of Lausanne, Switzerland, were retrospectively analyzed.

Charts were reviewed for clinical reports where a complete neurological examination was done and fully reported. Neurological abnormalities were subsequently classified as 1/ none, 2/ peripheral neuropathy, 3/ paresis/paralysis, 4/ seizures, 5/ coma.

Reports of neuroradiological investigations were reviewed and the abnormal ones classified into 4 different non-exclusive categories: 1/ Mild LE (one lobe) 2/ Severe LE (diffuse), 3/ Calcifications, 4/ Cerebral atrophy.

MBP levels were obtained at the time of each intrathecal injection planned according to the treatment protocol by collecting 1ml of CSF. MBP levels were measured in our neurochemistry laboratory by radioimmunoassay using a method described earlier [21;28]. Values above 2.5 ng/ml were considered abnormal.

Data on academic achievement were retrieved from our long-term follow-up database and from annual phone contacts with patients and families by our Clinical Research Associate (EG). Retrieved informations were then classified into either no schooling problems, mild problems needing repeating a year/academic support or severe problems needing scholarization in a special school.

Results

Between January 1981 and December 2001, 103 patients were treated for ALL at the unit of pediatric hematology/oncology in Lausanne and 98 charts were available for evaluation. One patient was subsequently excluded from analysis because he developed measles encephalitis which was deemed to be compromising the interpretation of MBP levels. Of the remaining 97 patients, 54 were males (55.7%) and 43 females (44.3%). Age at diagnosis ranged from 1.4 months to 14.7 years (median 55.5 months). Most of them had B-precursor ALL (80, 82.5%), 9 (9.3%) T-cell ALL, 7

(7.2%) non B- non T-ALL and one could not be classified. At diagnosis, 9 (9.3%) of our patients presented with CNS involvement. Fourteen (14.4%) underwent cranial irradiation (7/9 for initial CNS involvement, 7 as prophylaxis) as part of their treatment. The radiotherapy dose applied was 24Gy in nine (including 6 with CNS involvement), 20Gy in one, 18Gy in two and 12Gy in two patients. Regarding intrathecal therapy, 58 patients received triple intrathecal therapy (TIT: methotrexate, cytarabine and hydrocortisone), 12 received intrathecal methotrexate alone (IT), and 27 had a combination of TIT and IT. Overall 75 patients (77.3%) were alive at the end of the data collection time. The mean duration of follow-up was 92.2 months, ranging from 0.9 to 302 (median 79.3). We retrieved 1248 dosages of CSF MBP in 83 patients, 381 individual full neurological examinations in 34 patients and 69 neuroradiological investigations in 27 patients, 25 by CT and 44 by MRI.

Table 1 outlines the patients' characteristics and the number of evaluable patients in the groups with normal and abnormal MBP levels respectively. Sixty-two (74%) patients were evaluable for academic achievement, 30 with normal MBP levels and 32 with abnormal levels. Mean age at diagnosis for patients in the groups with and without school difficulties were similar (62.1 (SD: 45.7) and 62.2 (SD: 40.9) months). Mean number of MBP determinations were 17.4/patient (SD: 8.2) in the group with abnormal MBP levels and 10.4/patient (SD: 6.6) in the group with normal levels.

Figure 1 depicts the patients' distribution according to MBP level, imaging, clinical symptoms and academic achievement. Of the 97 patients, 83 (85.5%) had at least one MBP level done and 52 of them (62.7%) had at least one abnormal MBP level (above 2.5ng/ml).

Among the patients with an abnormal MBP level, 15 were radiologically investigated and 7 (47%) presented radiological anomalies, most of them (5/7) with signs of LE. Of those patients with LE, 4 had clinical symptoms, 2 with peripheral neuropathy and 2 with seizures. Among the same 5 patients, 3 had a normal scholar cursus and for 2, information was lacking. Five out of the 8 patients with normal imaging had neurological symptoms, 3 with peripheral neuropathy and 2 with seizures. Three of the 5

symptomatic patients were evaluable for academic achievement and had a normal cursus.

Thirty-seven patients had an abnormal MBP level but no imaging done. Informations on neurological symptoms were available in twenty out of those 37 patients. Six were asymptomatic while 14 presented neurological abnormalities, either peripheral neuropathy (7 patients), paresis (4 patients) and seizures (3 patients). Among those 20 patients, 6 were evaluable for academic achievement, 5 having a normal cursus and 1 presenting school difficulties.

Considering the long-term outcome in terms of school performances of this group of patients with abnormal MBP levels as a whole, informations were available in 32/52 patients (61.5%). Thirty (94%) of them had an academic achievement considered as normal and 2 had learning difficulties. Information was lacking in 20/52 (38.5%) patients.

Eleven patients of the 31 (35%) with a normal MBP level were investigated radiologically. Both patients with an abnormal imaging showing signs of LE had school difficulties and one of them had seizures. Among the nine remaining ones, 1 patient presented with a paresis and had a normal school cursus, 2 others had school difficulties but had a normal neurological exam and 6 were asymptomatic and had a normal academic cursus.

Among the 20 patients with a normal MBP level and no imaging done, none had clinical symptoms, 18 (90%) had a normal school cursus, 1 had school difficulties and for another one, information was lacking.

Looking at the academic achievement of this group of patient with normal MBP level as a whole, information was available in 30 patients (97%) with 25 (83.3%) going to normal school and 5 having learning difficulties. Information was lacking in one patient.

Follow up data were updated in 61/62 patients between December 2007 and December 2008. In the group with normal MBP, out of the 5 patients initially classified as having difficulties, 4 subsequently followed a normal scholar cursus without any problems. One patient originally categorized as having no problems developed minor difficulties with memorisation, but he is currently following a normal cursus. One patient was lost to follow up and one was confirmed as having difficulties at school. In the group with

abnormal MBP, two patients who were considered to have a normal cursus subsequently developed minor difficulties (minor attention deficit for one and some difficulties in mathematics for the other). One patient who was classified as having difficulties subsequently obtained a nurse degree without any trouble. Two patients had relapsed and died of their disease, one in each group.

Discussion:

Specificity and sensitivity of CSF MBP levels and their usefulness in predicting methotrexate-related neurotoxicity remains controversial [23;25;29;30]. As noted in these reports and in our study, increased MBP levels do not seem to correlate with CNS status at diagnosis, prophylactic cranial irradiation, sex or diagnosis. In our patients' population, there was a trend towards more abnormal radiological and clinical examinations with high MBP levels, but without a temporal association of abnormal CSF MBP levels and the occurrence of those neuroradiological or clinical abnormalities. This is supported by observations from other authors describing transient abnormalities of the white matter which resolved on subsequent neuroimaging studies[31].

Considering their long-term outcome in terms of school performances, among patients with at least one determination of CSF MBP, information was available in a good proportion (62 patients, 74.6%, 30 with normal MBP levels and 32 with abnormal levels). In the group with normal MBP levels, there was a slightly higher rate of reported learning difficulties compared to the group with abnormal MBP levels (16.7% versus 6%), although mean number of MBP determinations was smaller in the group with normal MBP levels (10.4 versus 17.4) which could potentially introduce a bias. Mean age at diagnosis for patients with and without school difficulties were similar (62.1 vs 62.2 months), but with large confidence intervals, especially in patients with school difficulties. Ochs reviewed in 1989 the different forms of neurotoxicity due to CNS prophylactic therapy and showed a 15% incidence of cerebral atrophy, 8.5% of cerebral calcifications and 3.5% of focal white matter hypodensities on CT scans. She showed as well that younger patients who received combined therapy with cranial irradiation and intrathecal methotrexate were at higher risk. However, the incidence of learning difficulties seemed to be greater than that of CT scan abnormalities [32]. Our observation that a substantial

proportion of patients with normal MBP and imaging presented with learning difficulties compared to the proportion of patients with any abnormalities suggests a relative weakness of both imaging technique and MBP levels in predicting such problems, but the overrepresentation of unevaluable patients in the group with abnormal MBP level could have potentially introduced a type 2 error in our conclusions.

The classification of schooling difficulties we used is subject to discussion as it was self reported, obtained by phone calls, and not taking into account other variables that could have influenced schooling, like treatment related complications leading to more school absenteeism, difficulties unrelated to the treatment, parental education, social support, etc. Nevertheless, although phone call use as a efficient and appropriate mean of academic achievement specific evaluation has not been evaluated to our knowledge, it has been generally accepted as a suitable tool for long-term follow-up of patients with cancer[33]. A "response rate" of 72.2% for the whole group of patients regarding informations about academic achievement, although not optimal, can probably be considered as satisfactory given the design of our study.

Notwithstanding the retrospective character of our study and its inherent difficulties in evaluation, especially with small numbers of patients, we conclude that there is limited usefulness of systematic dosage of CSF MBL levels as indicator of possible treatment-induced neurotoxicity in ALL patients, as elevated levels at some point during treatment are common, often without signs of clinical toxicity and little effect on long-term outcome such as learning abilities. Based on these results, we decided to stop the measurement of CSF MBP. A recent publication by Osterlundh et al. gives some clues about potential useful markers of CSF toxicities that could be used on a prospective manner in the future[34].

References

1. Evans AE, Gilbert E, Zandstra R. The increasing incidence of central nervous system leukemia in children. Cancer 1970; 26:404-09.

2. Pui CH, Evans WE. Treatment of Acute Lymphoblastic Leukemia. N Engl J Med 2006; 354:166-78.

3. Komp DM, Fernandez CH, Falletta JM et al. CNS prophylaxis in acute lymphoblastic leukemia: comparison of two methods - a Southwest Oncology Group study. Cancer 1982; 50:1031-36.

4. Littman P, Coccia P, Bleyer WA et al. Central nervous system prophylaxis in children with low risk acute lymphoblastic leukemia. Int.J.Radiation Oncology Biol.Phys. 1987; 13:1443-49.

5. Van Eys J, Berry D, Crist W et al. A comparison of two regimens for high-risk acute lymphocytic leukemia in childhood: a pediatric oncology group study. Cancer 1989; 63:23-29.

6. Nachman J, Sather HN, Cherlow JM et al. Response of children with high risk acute lymphoblastic leukemia treated with and without cranial irradiation: A report of the Children's Cancer Study Group. Journal of Clinical Oncology 1998; 16:920-30.

7. Pui CH. Central nervous system disease in acute lymphoblastic leukemia: prophylaxis and treatment. Hematology Am Soc Hematol Educ Program 2006;142-46.

8. Lo Nigro L, Di Cataldo A, Schiliro G. Acute Neurotoxicity in Children with B-Lineage Acute Lymphoblastic Leukemia (B-ALL) Treated with Intermediate Risk Protocols. Medical and Pediatric Oncology 2000; 35:449-55.

9. Mahoney DH, Shuster J, Nitschke R et al. Acute Neurotoxicity in Children With B-Precursor Acute Lymphoid Leukemia: An Association With Intermediate-Dose Intravenous Methotrexate and Intrathecal Triple Therapy-A Pediatric Oncology Group Study. Journal of Clinical Oncology 1998; 16:1712-22.

10. Quinn CT, Griener JC, Bottiglieri T et al. Elevation of homocystein and excitatory amino acid neurotransmitters in the CSF of children who receive methotrexate for the treatment of cancer. Journal of Clinical Oncology 1997; 15:2800-06.

11. Ochs J, Parvey LS, Mulhern R. Prospective Study of Central Nervous System Changes in Children with Acute Lymphoblastic Leukemia Receiving Two Different Methods of Central Nervous System Prophylaxis. Neurotoxicology 1986; 7:217-26.

12. Pizzo PA, Poplack DG, Bleyer WA. Neurotoxicities of current leukemia therapy. American Journal of Pediatric Hematology/Oncology 1979; 1:127-40.

13. Aur RJA, Simone JV, Verzosa MS. Childhood acute lymphoblastic leukemia. Study VIII. Cancer 1978; 42:2123-34.

14. Meadows AT, Evans AE. Effects of chemotherapy on the central nervous system - A study of parenteral methotrexate in long-term survivors of leukemia and lymphoma in childhood. Cancer 1976; 37:1079-85.

15. Kay HEM, Knapton PJ, O'Sullivan JP et al. Encephalopathy in acute leukemia associated with methotrexate therapy. Archives of Disease in Childhood 1972; 47:344-54.

16. Pochedly C. Prophylactic CNS therapy in childhood acute leukemia: a review of methods used. The American Journal of Pediatric Hematology/Oncology 1979; 1:119-26.

17. Freeman AI, Boyett JM, Glicksman AS et al. Intermediate-dose methotrexate versus cranial irradiation in childhood acute lymphoblastic leukemia: a ten year follow-up. Medical and Pediatric Oncology 1997; 28:98-107.

18. Waber DP, Silverman LB, Catania L et al. Outcomes of a randomized trial of hyperfractionated cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: therapeutic efficacy and neurotoxicity. Journal of Clinical Oncology 2004; 22:2701-07.

19. McLaurin J, Ackerley CA, Moscarello MA. Localization of Basic Proteins in Human Myelin. Journal of Neuroscience Research 1993; 35:618-28.

20. Bates SE, Raphaelson MI, Price RA et al. Ascending Myelopathy After Chemotherapy for Central Nervous System Acute Lymphoblastic Leukemia: Correlation With Cerebrospinal Fluid Myelin Basic Protein. Medical and Pediatric Oncology 1985; 13:4-8.

21. Bürgisser P, Matthieu JM, de Tribolet N et al. Dosage de la protéine basique de la myéline dans le liquide céphalo-rachidien au cours d'affection neurologiques. Schweizerische Medizinische Wochenschrift 1982; 112:643-47.

22. Cohen SR, Herndo RM, McKhann GM. Radioimmunoassay of myelin basic protein in spinal fluid. An index of active demyelination. New England Journal of Medicine 1976; 295:1455-57.

23. Ganji D, Reaman GH, Cohen SR et al. Leukoencephalopathy and elevated levels of myelin basic protein in the cerebrospinal fluid of patients with acute lymphoblastic leukemia. N Engl J Med 1980; 303:19-21.

24. Matthieu JM, Suardet L. Le chimisme du liquide céphalo-rachidien dans des affections neurologiques et psychiatriques. Médecine et Hygiène 1983; 41:3769-77.

25. Pagano L. Liquoral Myelin Basic Protein in Acute Lypmphoblastic Leukemia. Eur.J.Haematol. 1989; 42:407-08.

26. Surtees R, Clelland J, Hann I. Demyelination and Single-Carbon Transfer Pathway Metabolites During the Treatment of Acute Lymphoblastic Leukemia: CSF studies. Journal of Clinical Oncology 1998; 16:1505-11.

27. Mahoney DH, Fernbach D, Glaze DG et al. Elevated Myelin Basic Protein Levels in the Cerebrospinal Fluid of Children with Acute Lymphoblastic Leukemia. Journal of Clinical Oncology 1984; 2:58-61.

28. Cohen SR, Herndo RM, McKhann GM. Radioimmunoassay of myelin basic protein in spinal fluid. An index of active demyelination. New England Journal of Medicine 1976; 295:1455-57.

29. Pinkerton CR, Chessells JM, Hoyle NR. Myelin basic protein concentration in the CSF of children receiving methotrexate (letter). Journal of Clinical Oncology 1986; 4:112-13.

30. Thyss A. Myelin basic protein in CSF of children receiving intrathecal chemotherapy (letter). Journal of Clinical Oncology 1986; 4:1569.

31. Ochs J, Mulhern R, Fairclough D et al. Comparison of Neuropsychologic Functioning and Clinical Indicators of Neurotoxicity in Long-Term Survivors of Childhood Leukemia Given Cranial Radiation or Parenteral Methotrexate: A Prospective Study. Journal of Clinical Oncology 1991; 9:145-51.

32. Ochs J. Neurotoxicity due to central nervous system therapy for childhood leukemia. American Journal of Pediatric Hematology/Oncology 1989; 11:93-105.

33. Cox K, Wilson E. Follow-up for people with cancer: nurse-led services and telephone interventions. J.Adv.Nurs. 2003; 43:51-61.

34. Osterlundh G, Kjellmer I, Lannering B et al. Neurochemical markers of brain damage in cerebrospinal fluid during induction treatment of acute lymphoblastic leukemia in children. Pediatr.Blood Cancer 2008; 50:793-98.

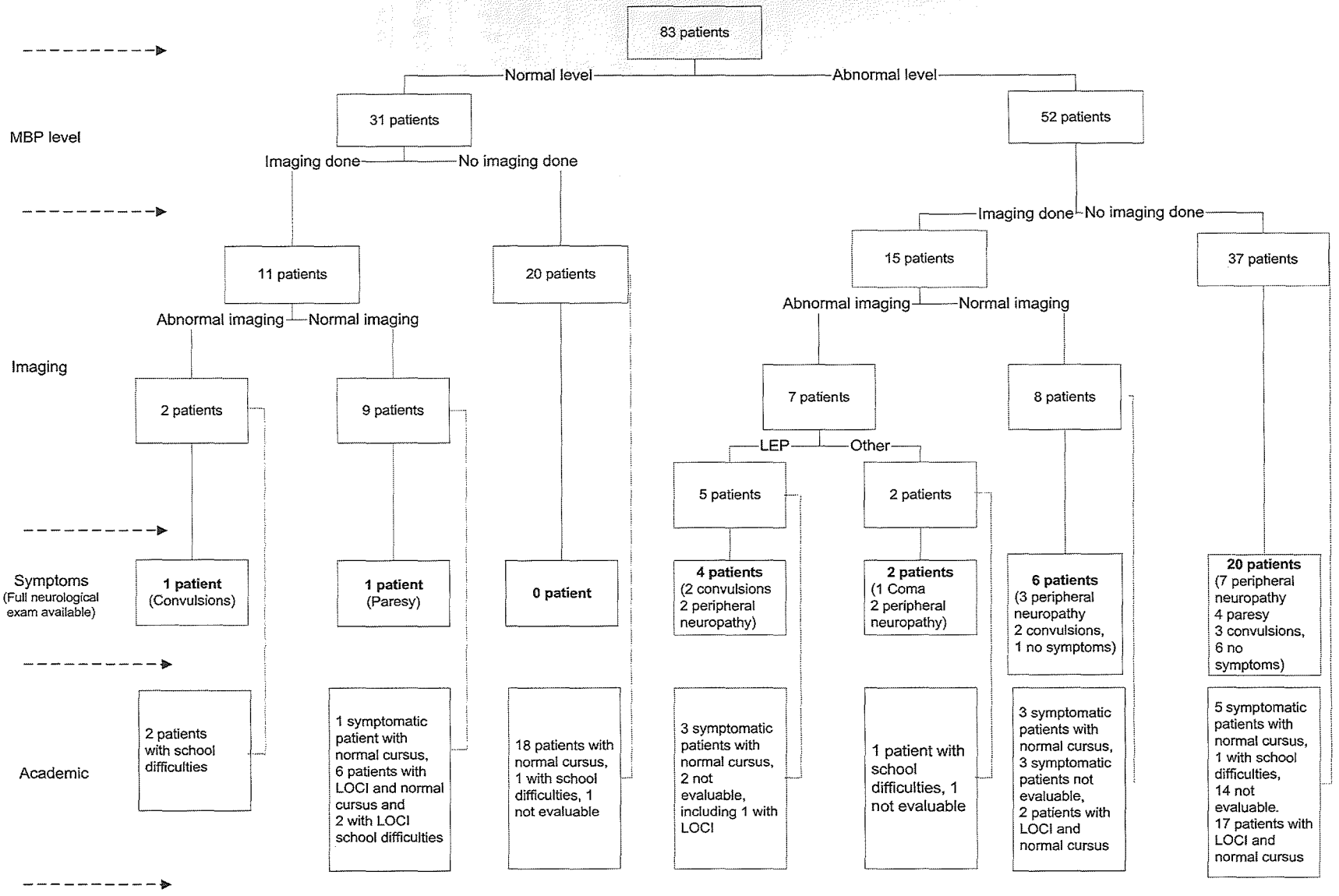

Fig. 1: Distribution of patients with at least one measurement of MBP level. LOCI: Lack of clinical information (Full neurological examination not available)

Fig. 1: Distribution of patients with at least one measurement of MBP level. LOCI: Lack of clinical information (Full neurological examination not available)

Table I : Demographics

	Normal MBP levels	Abnormal MBP levels	Total*
Number of patient	31	52	97
Age at diagnosis, months (mean, SD)	70.6, 44.0	60.4, 43.3	66.8, 44.5
Number of MBP determinations per patient (mean, SD)	10.4, 6.6	17.4, 8.2	12.6, 9.3
Number of patients with normal schooling	25 (80.6%)	30 (57.7%)	63 (64.9%)
Number of patient evaluable for schooling	30 (97%)	32 (61.5%)	70 (72.2%)
Number of patients with radiological investigations	11 (35%)	15 (32.6%)	27 (27.8%)
Number of patients with clinical evaluation	2 (6.4%)	25 (48%)	34 (35%)
Number of patients with CNS XRT	2 (6.4%)	10 (19.2%)	14 (14.4%)
Number of patients with CNS disease	1 (3.2%)	7 (13.4%)	9 (9.3%)
Diagnosis			
PreB-ALL	30 (97%)	38 (73%)	80 (82.5%)
T-cell ALL	1 (3.2%)	7 (13.4%)	9(9.3%)
Non B non T ALL	0	7 (13.4%)	7(7.2%)
Not classified	0	0	1 (1%)

*Including patients with no MBP determination