0021-7557/06/82-04/273
Jornal de Pediatria

doi:10.2223/JPED.1512

ORIGINAL ARTICLE

Prospective study of 11 Brazilian patients with mucopolysaccharidosis II

Louise L. C. Pinto,[1] Ida V. D. Schwartz,[1] Ana C. S. Puga,[2] Taiane A. Vieira,[2] Maria Verônica R. Munoz,[2] Roberto Giugliani[1]; MPS II Study Group[3]

Abstract

Objective: To assess the progression of mucopolysaccharidosis II in 11 Brazilian patients over a 12-month period.

Methods: Eleven Brazilian patients with mucopolysaccharidosis II were prospectively studied at the Division of Medical Genetics of Hospital de Clínicas de Porto Alegre. The initial assessment and the assessment at 12 months included: anamnesis, physical examination, abdominal nuclear magnetic resonance, echocardiogram, 6-minute walk test, audiometry, serum biochemical tests and urinary glycosaminoglycan concentration.

Results: The major findings after comparing the assessments were: 1) two patients had growth retardation; 2) two patients showed negative weight change; 3) one patient went from obese to overweight; 4) three patients revealed left ventricle hypertrophy; of these, two increased the number of cardiac valve lesions; 5) there was no statistically significant difference between the mean distances obtained on the 6-minute walk test; 6) there was splenic enlargement; 7) there was an increase in gamma-glutamyltransferase levels; 8) the urinary concentration of glycosaminoglycans remained unchanged.

Conclusions: In general, echocardiographic findings were the only variable with deterioration and possible immediate clinical consequences. Although a 12-month period is too short to detect changes in most variables related to mucopolysaccharidosis II, its progressive nature should be taken into account when evaluating the efficiency of treatment protocols.

J Pediatr (Rio J). 2006;82(4):273-8: Glycosaminoglycans, mucopolysaccharidosis II, Hunter syndrome, iduronate sulfatase.

Introduction

Mucopolysaccharidoses (MPS) are a group of genetic diseases caused by the lack of one of the lysosomal enzymes in charge of a specific stage of glycosaminoglycan (GAG) degradation. Mucopolysaccharidosis II (MPS II or Hunter syndrome) is X-linked, and results from the deficiency of iduronate sulfatase (IDS), with consequent increase in the urinary concentration of dermatan sulfate and heparan sulfate.[1] According to international studies, MPS II is estimated to affect 1 in every 68,000 to 1 in every 320,000 live births.[2,3] Although accurate data are not available on the incidence of MPS in Brazil, MPS II seems to be one of the most frequently diagnosed types of this disease in Brazil. At the Laboratory of Inborn Errors of Metabolism of the Division of Medical Genetics of Hospital de Clínicas de Porto Alegre, a referral laboratory for the diagnosis of MPS in Brazil, 104 Brazilian MPS patients were diagnosed between April 2004 and September 2005. The following types were diagnosed: MPS I (33 cases), MPS II

1. Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brasil. Programa de Pós-Graduação em Genética e Biologia Molecular, Departamento de Genética, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brasil.
2. Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brasil.
3. MPS II Study Group: Silvia Brustolin, Adriana Pires, Maria Ângela Moreira, Patrícia Barrios, Simão Piltcher, Letícia Schmidt, Luciana Cigana, Leonardo Vedolin, Raquel Boy, Emerson Santos, Marcia Ribeiro, Denise Norato, Ruy Oliveira Sobrinho, Angelina Acosta, Julie Lieb, Anne Conway; Serviços de Pneumologia, Cardiologia e Otorrinolaringologia do Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brasil; Serviço de Radiologia, Hospital Mãe de Deus Center, Porto Alegre, RS, Brasil; Departamento de Pediatria, Universidade Estadual do Rio Janeiro (UFRJ), Rio de Janeiro, RJ, Brasil; Departamento de Pediatria, Fundação Universidade de Ciências da Saúde de Alagoas, Maceió, AL, Brasil; Instituto de Puericultura e Pediatria Martagão Gesteira, UFRJ, Rio de Janeiro, RJ, Brasil; Departamento de Genética Médica, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brasil; Departamento de Genética, Universidade Federal da Bahia (UFBA), Salvador, BA, Brasil; Transkaryotic Therapies Inc., Cambridge, USA.

Manuscript received Nov 08 2005, accepted for publication Mar 17 2006.

Suggested citation: Pinto LL, Schwartz IV, Puga AC, Vieira TA, Munoz MV, Giugliani R, et al. Prospective study of 11 Brazilian patients with mucopolysaccharidosis II. J Pediatr (Rio J). 2006;82:273-8.

(25), MPS III (14), MPS IV (12), MPS VI (18) and MPS VII (2).[4]

Most of the literature on MPS II concerns case reports and/or case series that include patients with other types of MPS.[5-8] Studies about the natural history of MPS II are rare and the existing ones use a retrospective approach;[9] patients are often normal at birth, and the progressive course of the disease is the general rule, even though the stages of progression have not been clearly defined in the literature.[1,10] The most common clinical signs are coarsening of facial features, skeletal disorders, short stature, joint stiffness, impaired neuropsychomotor development, recurrent airway infections, deafness, and cardiopathy. Corneal opacity and thoracolumbar kyphosis are not common. Papular lesions on the back, arms and buttocks are characteristic of MPS II and seldom occur in other types of MPS.[11,12] Skeletal disorders are collectively known as dysostosis multiplex and include macrocephaly, J-shaped sella turcica, reduction of the anteroposterior diameter of vertebrae, coxa valga, irregular formation of the diaphysis of long bones and epiphyseal dysplasia of short tubular bones. MPS II is associated with different clinical entities and is usually classified, according to the presence of growth retardation and/or mental retardation, into neuronopathic or non-neuronopathic.[10]

The present study aimed to assess the progression of MPS II in 11 Brazilian patients over a one-year period, and to investigate the natural history of this type of MPS and of its progression.

Material and methods

This study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre and carried out in compliance with the recommendations for clinical research. All patients and/or surrogates signed an informed consent form before the study. According to the inclusion criteria, the patients should be male, have deficiency of IDS in the plasma and/or leukocytes and normal activity of another sulfatase, and should not have received specific treatment for MPS II (bone marrow transplantation or enzyme replacement therapy). Potential participants were recruited from the Outpatient Clinic of MPS of the Division of Medical Genetics (Serviço de Genética Médica, SGM) of HCPA, a Brazilian referral center for the diagnosis and treatment of these diseases. Since 1998, this outpatient clinic has attended to nearly 100 MPS patients, from several Brazilian states. The study design allowed for the inclusion of 20 patients, approximately 50% of whom had the neuronopathic form of MPS II. The assessments were made through two visits to the SGM of HCPA; the first one, moment 0 (1st visit), and the second one, 12 months afterwards (2nd visit), and included: anamnesis, physical examination, abdominal magnetic resonance to measure the volume of the liver and spleen, echocardiogram, 6-minute walk test (6MWT), audiometry, serum biochemical tests, and quantification of urinary GAG concentration. In an attempt to minimize possible assessment biases, the same researchers of each area made the assessments. In the 1st visit, the patients were submitted to psychological tests for evaluation of their development and intelligence quotient, so that they could be categorized either as having the neuronopathic or non-neuronopathic form of MPS II.

Both patients and their parents or surrogates were interviewed (anamnesis), where the following information was collected: date of birth, city of origin, age at the moment of assessment, medications continuously used, walking capacity, presence of blindness, use of continuous positive airway pressure (CPAP) and history of tracheostomy. On physical examination, anthropometric measurements (weight, height, head circumference) and presence of papular lesions that are characteristic of MPS II were analyzed. Upper abdominal magnetic resonance was used to determine the volume of the liver and spleen. Liver and spleen volumes were checked against normal values by using the criteria developed by Weinreb et al.[13]

The 6MWT was performed on two alternate days in both visits (totaling four tests) and according to the American Thoracic Society recommendations.[14] The head circumference percentiles were calculated by using the standard Nelhaus curve.[15] In the case of anthropometric measurements, indicators were expressed as z score,[16,17] and the National Center of Health Statistics (NCHS)[18] curve was used as reference. Height/age (H/A), weight/age (W/A) and weight/height (W/H) were subdivided into the following parameters: < -2 z score (height deficit), -2 to -1 z score (nutritional risk), -1 to +1 z score, +1 to +2 z score and > +2 z score. Epi-Info 6.0 was used for the analysis of this variable.

According to the study protocol, development was assessed in patients aged 3 to 10 years, and the intelligence quotient, in patients older than 11 years. The assessment of development included the following tests: Bayley Scales of Infant Development – Second Edition (BSID-II) (children up to 42 months of age)[19] and the Weschsler Preschool and Primary Scale of Intelligence – Revised (WIPPSI-R)[20] (children between 43 months and 10 years old). The Leiter-R[21] test was used for the intelligence quotient. Patients with abnormal results in the assessment of development and/or on the intelligence quotient test were regarded as having neuronopathic MPS II.

The statistical analysis was carried out using SPSS 11.0 and NCSS 5.0. The continuous variables were compared, between the two visits, by way of a *t* test for nonparametric samples (Wilcoxon's test). A p value of 0.05 was regarded as statistically significant. Both SPSS 11.0 and NCSS 5.0 programs were used for the tests.

Only those variables obtained from at least 50% of the patients were considered in this study.

Results

Twenty patients participated in the study. However, six of them (all with the non-neuronopathic form of the disease), were excluded, since they had begun enzyme replacement therapy, and three patients did not show up for the second visit (one died, whereas the clinical condition of two remarkably deteriorated). The three patients who did not show up for the second visit had the neuronopathic form of the disease. Therefore, the assessment regarding the second visit was only carried out in 11 patients, and only data from this group were used in the present study. These patients came from the Southeast (36.4%), Northeast (36.4%) and South (27.2%) regions of Brazil. Some neurological involvement was observed in 10 out of 11 patients, characterizing the neuronopathic form of MPS II and explaining the lack of adherence to some assessments, as determined by the study protocol. The results are shown in Tables 1, 2 and 3.

The analyzed sample basically consisted of children. In the first visit, the mean age was 7.3 years (SD ± 3.6) and in the second visit, it was 8.4 years (SD ± 3.6). Only one patient had the non-neuronopathic form (11.2 years) of MPS II, being submitted to the IQ test.

The anamnesis during the first visit provided the following data: 10 in 11 patients showed normal autonomous walking, no patients presented with blindness, 1 in 11 was submitted to CPAP, 1 in 11 used cardiac medications. The anamnesis during the second visit originated the following data: 9 in 11 patients showed normal autonomous walking, no patients presented with blindness, 1 in 11 was submitted to CPAP, and 2 in 11 used medications to treat cardiac manifestations of the disease. The physical examination revealed that the mean head circumference was 55.5 cm (SD ± 1.97) in the first visit and 56.1 cm (SD ± 1.44) in the second visit. On physical examination during the first visit, 3 out of 11 patients had papular lesions, whereas during the second visit, 4 of 11 patients had these lesions.

In the 11 patients assessed, worse results were observed for the following assessments and tests: H/A (4/7); W/A (4/7); deterioration of echocardiographic results (3/11); splenomegaly on abdominal resonance (3/11) and increase in serum gamma-glutamyltransferase (gamma-GT) levels (4/11) (Table 1).

On the other hand, the following variables analyzed in this period remained unchanged: mean urinary GAG concentrations, mean distances walked in the 6MWT, liver volume and other serum biochemical tests (Table 2).

Table 1 - Distribution of weight, age and height indicators in patients with mucopolysaccharidosis type II (n = 11)

Indicator	1st visit (n = 7/11)	2nd visit (n = 7/11)
Height/age		
< -2 z score (height deficit)	1	3
-2 to -1 z score (nutritional risk)	2	2
-1 to +1 z score	2	1
+1 to + 2 z score	2	1
> + 2 z score	0	0
Weight/age		
< -2 z score (height deficit)	1	1
-2 to -1 z score (nutritional risk)	1	2
-1 to +1 z score	0	1
+1 to + 2 z score	2	1
> + 2 z score	3	2
Weight/height		
< -2 z score (height deficit)	0	0
-2 to -1 z score (nutritional risk)	0	0
-1 to +1 z score	0	0
+1 to + 2 z score	2	3
> + 2 z score	5	4

Four patients were excluded from the analysis due to inappropriate conditions for weight and height measurements.

Discussion

This is the first prospective study carried out in patients with MPS II. Although the collected data are related to the 11 patients who showed up for the first and second visits, we underscore that, in this 12-month period, there was a remarkable clinical deterioration of other three patients with the neuronopathic form of MPS II, who had been previously included in the study (including one who died), which highlights the progressive course of this disease.

The analyzed sample basically consisted of children who had the neuronopathic form of MPS II. This may have occurred due to the fact that: 1) the neuronopathic form is the most frequent form in MPS II;[8] 2) since patients were selected at a referral center, more severely ill patients might have shown a greater interest in participating in this study because they were already being followed up at the outpatient clinic. It should be noted that two neuronopathic and non-neuronopathic subtypes cannot be distinguished through biochemical results,[22] and therefore, intellectual deterioration should be the major criterion for the classification of patients into these subgroups.[11] It is worth mentioning that the tests carried out in these patients are not specific to the assessment of patients with Hunter syndrome. The reason why we included the patient with the non-neuronopathic form of the disease in our analysis is that neurological involvement does not predict more severe involvement of other areas.

Table 2 - Natural history of mucopolysaccharidosis II: assessments made in a sample of Brazilian patients (n = 11)

Assessments	n	1st visit * results	2nd visit * results
Echocardiogram	10/11		
Normal		1/10	1/10
Aortic valve disease		7/10	7/10
Mitral valve disease		6/10	07/10/06
Tricuspid valve disease		01/10	02/10
Normal ejection fraction		9/10	9/10
Left ventricle hypertrophy		1/10	4/10
Six-minute walk test (m)	6/11		
Test 1 (mean ± SD)		308.3±45.6	349.0±74.6
Test 2 (mean ± SD)		336.5±67.2	334.5±61.0
Audiometry	7/11		
Hearing loss		7/7	7/7
Abdominal resonance (cm^3)	7/11		
Liver volume (mean ± SD)		604.6±101.4	615.3±63.3
Hepatomegaly		0/7	0/7
Splenic volume (mean ± SD)		172.9±81.8	269.1±129.9
Splenomegaly		1/7 †	4/7 †
Urinary glycosaminoglycan concentration ‡	10/11		
Number of times above the upper normal limit (mean±SD)		5.4±2,3	7.4±5.7

SD = standard deviation.
* The interval between the 1st and 2nd visits was of approximately 12 months.
† $p < 0.05$.
‡ Normal urinary glycosaminoglycan levels vary with age.

Of the 11 patients analyzed, only seven could be evaluated in terms of z score, for two reasons: 1) we could not measure the height of two patients due to remarkable joint stiffness; 2) the other two patients were aged 11 and 14 years, and could not be assessed by these criteria. The results should be interpreted with caution, since these patients have short stature in a given moment of their linear growth when compared to normal values for their age. The time at which stunted growth begins in these patients has not been clarified, so further studies with a longer time span and a larger number of assessments are necessary. Regarding weight, since these patients have short stature, the relationship of this variable with another parameter (e.g. height/age) should also be interpreted with caution. For some syndromes, there are specific curves for assessment, providing more accuracy to anthropometric data. Even though nutritional variables were not assessed in our study, the results suggest that these children should be assessed in terms of nutrition as well.

In general, echocardiographic findings were the only variable that showed deterioration with possible immediate clinical consequences. Other variables that showed progression (herein defined as deterioration of preexisting lesions or the development of new ones) were height, papular skin lesions, splenic volume and gamma-GT levels (Tables 1, 2 and 3). Despite the progressive course of the disease, the 12-month period was not long enough to detect abnormalities in the remaining parameters.

6MWT and the quantification of urinary GAG levels have been used as outcomes in studies assessing the efficiency of enzyme replacement therapy for MPS I and MPS VI[23,24] – the increase in the distance walked in the 6MWT and a decrease in GAG levels indicate recovery of the patient, as a result of treatment. In the absence of specific treatment, we may expect improvement of 6MWT results (due to improved application of the test, which originates from better information about the patient, combined with the increase in age), its stabilization, or its deterioration. 6MWT is a functional test[14,25] that is part of the assessment of cardiopulmonary and joint disorders of these patients. We did not find any statistically significant difference (*t* test for nonparametric samples) between the mean distances walked in both visits (Table 2), which suggests that the deterioration of echocardiographic results has not caused functional deterioration in the analyzed period. In our sample, 54% (6/11) of patients were able to perform the 6MWT, but most of these patients were not collaborative due to their cognitive deficit, so we only considered those patients who completed the exercise on

Table 3 - Natural history of mucopolysaccharidosis II: biochemical investigation of a sample of Brazilian patients (n = 11)

Tests	Abnormalities (n)	1st visit * Mean±SD	Abnormalities (n)	2nd visit * Mean±SD	Abnormalities (n)
LDH (U/L)	9/11	331.5±129,1	8/9	248.2±47.3	6/9
AST (U/L)	11/11	39.8±11.4	4/11	39.4±10.7	4/11
ALT (U/L)	11/11	32.5±11.4	2/11	38.9±17.6	4/11
Cholesterol (mg/dL)	11/11	165.1±36.2	2/11	168.8±56.8	2/11
Gamma-GT † (U/L)	11/11	22.5±13.0	0/11	46.2±29.0	4/11
Glucose (mg/dL)	11/11	95±7.0	1/11	85.4±9.1	0/11
Alkaline phosphatase (U/L)	11/11	577.2±240.6	1/11	516.2±188.7	0/11

ALT = alanine aminotransferase; AST = aspartate aminotransferase; gamma-GT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; SD = standard deviation.
* The interval between the 1st and 2nd visits was of approximately 12 months.
† $p < 0.05$.
Reference values (General Laboratory, Hospital de Clínicas de Porto Alegre): LDH 230-460U/L; ALT 10-40U/L; AST 15-40U/L; cholesterol < 200 mg/dL; gamma-GT 2-30U/L; glucose 70-100 m/dL; alkaline phosphatase (up to 15 years of age) < 640U/L.

two alternate days. As shown in Table 2, the distance walked in the 6MWT tends to be smaller on the first test (test 1 during the first visit), suggesting patient's learning.

With regard to urinary GAG, we noted that there was an apparent increase in its excretion, but we believe that this finding might have been influenced by the results obtained from a single patient, in whom this variable remarkably increased during the second visit.

In conclusion, our findings suggest that regular echocardiograms should be performed at least once a year in patients with MPS II and that other follow-up studies are necessary in order to establish guidelines for the assessment of these patients. The progressive nature of MPS II, confirmed by the present study, should be taken into account when assessing the efficiency of treatment protocols.

Acknowledgements

This study was part of an international collaborative study supported by Transkaryotic Therapies (TKT). We acknowledge the support received from CAPES, which awarded a grant to Dr. Louise Lapagesse de Camargo Pinto for her master's studies.

References

1. Neufeld EF, Muenzer J. The mucopolysaccharidosis. In: Scriver CR, Beandet AL, Sly S, Valle D, Childs B, Kinzler KW, Volgesltein B, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill; 2001. p. 3421-52.
2. Nelson J, Crowhurst J, Carey B, Greed L. Incidence of the mucopolysaccharidoses in Western Australia. Am J Med Genet A. 2003;123:310-3.
3. Online Mendelian Inheritance in Man (OMIM) [website]. Baltimore: Johns Hopkins University. http://www3.ncbi.nlm.nih.gov/omim. Access: 30/05/2006.
4. Giugliani R, Schwartz I. MPS Brazil Network: an alternative approach to improve diagnosis of metabolic disorders in developing countries. J Metab Genet. 2006 (In Press).
5. Muenzer J. Mucopolysaccharidoses. Adv Pediatr. 1986;33: 269-302.
6. Whitley CB. The mucopolysaccharidoses. In: Beighton P, editor. McKusick's Heritable Disorders of Connective Tissue. St Louis: Mosby; 1993. p. 367-498.
7. Lonergan CL, Payne AR, Wilson WG, Patterson JW, English JC 3rd. What syndrome is this? Hunter Syndrome. Pediatr Dermatol. 2004;21:679-81.
8. Albano LM, Sugayama SS, Bertola DR, Andrade CE, Utagawa CY, Puppi F, et al.. Clinical and laboratorial study of 19 cases of mucopolysaccharidoses. Rev Hosp Clin Fac Med Sao Paulo. 2000;55:213-8.
9. Young ID, Harper PS. The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. Dev Med Child Neurol. 1983;25:481-9.
10. Young ID, Harper PS, Archer IM, Newcombe RG. A clinical and genetic study of Hunter's syndrome. 1. Heterogeneity. J Med Genet. 1982;19:401-7.
11. Knoell KA, Tunnessen WW Jr. Picture of the month. Hunter syndrome (mucopolysaccharidosis IIA). Arch Pediatr Adolesc Med. 2000;154:85-6.
12. Demitsu T, Kakurait M, Okubo Y, Shibayama C, Kikuchi Y, Mori Y, et al. Skin eruption as the presenting sign of Hunter syndrome IIB. Clin Exp Dermatol. 1999;24:179-82.
13. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med. 2002;113:112-9.
14. ATS Committee on proficiency standards for clinical pulmonary function laboratories. American Thoracic Society Statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-7.
15. Nelhaus G. Head circumference from birth to eighteen years: practical composite international and interracial graphs. Pediatr. 1968;41:106-14.
16. Motta MEFA, Silva GAP. Desnutrição e obesidade em crianças: delineamento do perfil de uma comunidade de baixa renda. J Pediatr (Rio J). 1977;4:288-293.

17. Hamil PV, Drizd TA, Jonhson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center of Health Statistics percentiles. Am J Clin Nutr. 1979;32:607-29.
18. World Health Organization. Physical status: the use and the interpretation of anthropometry. Tech Rep Ser 854. Geneva: WHO; 1995.
19. Black MM, Matula K. Essentials of Bayley Scales of Infant Development II Assessment. New York: Wiley; 1999.
20. Weschler D. WPPSI-R Manual Wechsler preschool and primary scale of intelligence-revised. New York: Psychological Corporation; 1989.
21. Roid GH, Miller LJ. A totally non-verbal intelligence & cognitive abilities test. St. Louis: Stoelting; 2000.
22. Schwartz IVD. Estudo clínico, bioquímico e genético de pacientes com mucopolissacaridose tipo II e de possíveis heterozigotas [thesis]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2004.
23. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blind, placebo-controlled, multinational study of recombinant á-L-iduronidase (Laronidase). J Pediatr. 2004;144:581-8.
24. Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda MC, et al. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine 4-sulfatase. Pediatrics. 2005;115:e681-9.
25. Solway S, Broocks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest. 2001;119:256-70.

Correspondence:
Louise L. C. Pinto
Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2350
CEP 90035-003 – Porto Alegre, RS – Brazil
Tel.: +55 (51) 2101.8011 – Fax: +55 (51) 2101.8010
E-mail: loulapagesse@ibest.com.br