INCIDENCE DES MUCOPOLYSACCHARIDOSES EN TUNISIE

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RÉSUMÉ

The mucopolysaccharidoses (MPS) are a devastating heterogenous group of lysosomal storage disorders. To date no comprehensive study has been performed on the prevalence of lysosomal storage disorders in the Tunisian population. In order to create an epidemiological profile of MPS in Tunisia, we conducted a retrospective epidemiological survey covering the period 1970-2005. Multiple sources were used to identify affected patients. Ninety six confirmed MPS cases were collected from 132 suspected cases found in the surveyed data. Of the ninety six confirmed cases, 20% were from multiplex families. Consanguinity was found in 83% of the families. The crude rate for all types of mucopolysaccharidoses was 2.3 cases in 100,000 live births. The prevalence of MPS type I, III and IV, those most frequently occurring in the collected data, were estimated at 0.63, 0.7 and 0.45 per 100,000 live births, respectively. The cumulative incidence of MPS type VI (0.3 per 105 live births) was higher than reported in European countries; but, it is likely that the reported frequency of all types of MPS in Tunisia is underestimated.

MOTS-CLÉS

Mucopolysaccharidoses- Epidemiology- Tunisia

SUMMARY

Les mucopolysaccharidoses (MPS) constituent un groupe hétérogène dévastateur de maladies de surcharge lysosomale. Aucune étude à large échelle n'a été réalisée à ce jour pour évaluer l'ampleur épidémiologique de ces affections dans la population tunisienne. Nous avons mené, dans le but d'approcher la prévalence des différents types de mucopolysaccharidoses en Tunisie, une étude multicentrique nationale rétrospective couvrant la période 1970-2005. Plusieurs sources de données ont été consultées. Nous avons identifié 96 cas confirmés de MPS à partir de 132 cas suspectés. La consanguinité est retrouvée chez 80% des familles. Vingt pour cent des familles sont multiplex. Une augmentation significative des cas diagnostiqués est relevée depuis 1988. La prévalence globale de toutes les MPS est de 2.3/100.000 naissances vivantes. La prévalence des MPS de type I, III et IV ; types les plus fréquents de la série a été estimée à 0.63, 0.7 et 0.45 pour 100,000 naissances vivantes. La prévalence de la MPS de type VI (0.3 pour 105 NV) était plus élevée par rapport aux populations européennes. Malgré que le recouvrement a été le plus large possible nous estimons que la prévalence des différents types de MPS trouvée est sous estimée si l'on tient compte du taux de consanguinité dans la population tunisienne. L'amélioration des moyens de diagnostic et la mise en place de registre relatif à ces pathologies permettraient d'évaluer avec précision l'ampleur de ces affections graves et d'établir des stratégies thérapeutiques.

KEY-WORDS

Mucopolysaccharidoses- Epidémiologie -Tunisie

The mucopolysaccharidoses (MPS) are a heterogenous group of lysosomal storage disorders caused by deficiency of the enzymes involved in the degradation of glycosaminoglycans, resulting in organ dysfunction (1). During the past decade, the understanding of the molecular basis and the varied clinical manifestations of MPS has greatly evolved. The overall prevalence of the MPS disorders is difficult to estimate because of the scarcity of population-based studies and epidemiologic data (2-8). Accurate values for prevalence are required to accurately assess the cost of these disorders to public health care systems. Disease registries related to MPS will contribute to document the natural history of these disorders in various populations (9-10).
We report here a retrospective epidemiological survey of the MPS cases in Tunisia to estimate the cumulative incidences of the different types.

PATIENTS AND METHODS

In order to ensure the inclusion in this survey of all cases of MPS in Tunisia during the study period, three main sources were utilised:
1- Patient records from all departments likely to treat MPS throughout Tunisia: 11 paediatric, 1 infantile orthopaedic and two neurologic departments. Retrospective data were collected using a questionnaire designed to cover epidemiological features, diagnosis means and survival rates in affected patients.
2- Data of patients diagnosed before 1982 were collected from a medical doctoral thesis (Trabelsi M.) dealing with 23 cases of MPS in whom confirmation by urinary Glycoaminoglycans analysis (GAGs) or enzymatic assay were performed in a French laboratory (Pr Maroteaux).
3- Records from the two referral biochemical laboratories involved in the screening of MPS in Tunisia were searched thoroughly. The first of these labs, Farhat Hached, located in central Tunisia began MPS screening in 1988. The second lab, La Rabta, in the north of the country, began MPS screening in 1999. Analysis of urinary GAGs was based on qualitative and quantitative measurements (11-12). Enzymatic assays were performed in European laboratories (France, Belgium).
All patients with clinical and radiological phenotypes compatible with MPS diagnosed between 1970 and 2005 were included in the survey. Only MPS patients whose diagnosis was based on urinary GAGs's analysis and/or appropriate enzymatic assay within the period 1988 to 2005 were considered in the calculation of the prevalence. For epidemiological analysis, the crude occurrence rates were approximated by dividing the total number of cases by the total number of births during the study period. Data on the number of births in Tunisia were collected from the Tunisian institute of statistics (INS). Descriptive statistics were analysed using SPSS for windows (version 10.0).Frequencies'Comparison was based on the chisquare for linear trend test.

Results

Our survey covered the majority of paediatric departments in Tunisia and the two centers involved in the screening of MPS. Only three contacted departments, including a genetic laboratory not involved in the genetic investigations of such disorders, didn't participate in the study.
Of the 132 suspected MPS cases recorded in Tunisia during the period 1970-2005, there were 96 confirmed MPS patients, belonging to 80 families. Twenty one of the remaining 36 suspected MPS patients had the characteristic Morquio phenotype. Of the 96 confirmed cases, there were 52 boys and 45 girls. Consanguinity was found in 83% of the affected families. Twenty one percent of the families were multiplex, with 88% of these having two affected siblings. Demographics were available for 67 of the 80 affected families. Forty two percent (28/67) of the affected families originated from the north and the capital of Tunisia. The remaining families were equally distributed in the center (20/67) and the south (19/67). However, relative to population size, there was no significant difference in the frequency of MPS between the three regions of the country (p: 0.33).
The number of diagnosed incidents of MPS in Tunisia has significantly increased since 1988(p=0.004). Sixty percent of cases were diagnosed during the last ten years of the study period, with 30 patients diagnosed during the five last years. The number of patients with the various types of MPS for the period 1970-2005 is shown in table 1. The live births registered at the INS in the period from 1988 until 2005 numbered 3,309,091. The incidence rates of the various types of MPS in the same period are shown in Table 2.

Tableau 1: Distribution of Mucopolysaccharidoses (1970-2005)

Disease	Number	% of total
MPS I	**24**	**25**
Hurler phenotype	18	
Hurler/Scheie phenotype	6	
MPS II	**8**	**8**
MPS III	**30**	**32**
Type A	3	
Type B	9	
Type C	5	
Type ?	13	
MPS IV	**20**	21
Type A	10	
Type B	1	
Type?	9	
MPS VI	13	**13**
MPS I or II	1	**1**
All Mucopolysaccharidoses	**96**	

Tableau 2: Crude incidence rates (CIR) of the Mucopolysaccharidoses in Tunisia (1988-2005)

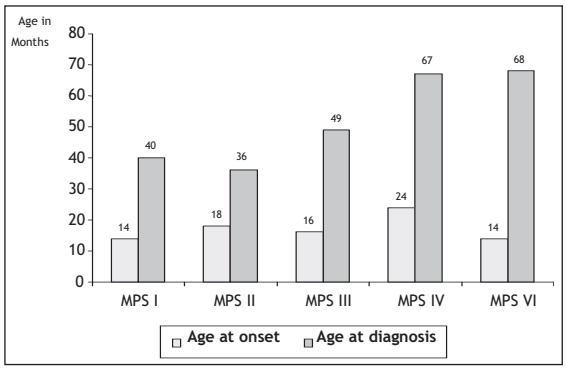
Type	Number of cases	Incidence (per total live births)	CIR Incidence (per 105total live births)
MPS I	22	1/ 159.000	0.63
MPS II	5	1/346.000*	0.29*
MPS III	24	1/143.000	0.7
MPS IV	15	1/223.000	0.45
MPS VI	10	1/ 333.000	0.35
Total	76	1/44.000	2.29

* Incidence of MPS II in terms of male live births

Of the 96 confirmed patients, 86% had urinary GAGs' analysis. Enzymatic assay was done in 58% of the cases. Six families with MPS type I, and four with MPS type IV had molecular analysis.

For all 96 confirmed MPS cases, the mean age at first symptoms and the mean delay for diagnosis were 18 and 34 months, respectively. Figure 1 shows the distribution of age at onset and at diagnosis in the various subtypes of MPS.

Figure 1: Mean age at first symptoms and at diagnosis of MPS types.



At the end of the study period, 60% of the patients were still alive and 10% were dead. The status of the remaining patients was not able to be determined. The ten years cumulative survival for MPS I and III was 50% and 86%, respectively. None of the patients had specific enzymatic therapy or bone marrow transplantation.

DISCUSSION

The mucopolysaccharidoses (MPS) represent the largest group of lysosomal storage disorders (LSD). In one study, this group comprised 53% of the 130 patients investigated with LSD within the period 1974-2000 in Tunisia (13). African epidemiological data about MPS are scarce. Forty seven MPS cases from the center and the south of Tunisia were diagnosed in the first referral laboratory involved in screening LSD (14). In Morocco, fourty seven MPS patients were investigated in the inborn metabolic errors center in Rabat over a period of 9 years (Talbaoui et al. Maroccan experience 1996-2004, SSIEM September 2005).

Our multicenter survey was the largest ever conducted in Tunisia. Although our survey was as thorough as possible, we are aware that the number of MPS cases collected was underestimated. Urinary GAG's screening, possible in only two laboratories for 10 million inhabitants, and enzymatic assays not yet performed in Tunisia, often make diagnosis difficult.

The crude incidence rate for all types of MPS was 2.3 per 105 total live births (1/44,000 live births). This is lower than the crude cumulative rates of 3.4 - 4.5 in 100,000 live births reported in European populations (15). In actuality, a higher incidence rate is predictable in Tunisia, taking into account the high rate of consanguineous marriages in Tunisia, which has been evaluated at 32% of the general population and reaches up to 80% in MPS families (16). This difference cannot be explained solely by the varying in populations' size, nor study design. What is more likely is that many cases of MPS in Tunisia were not diagnosed before 1990 and even to this day many cases are not properly diagnosed. Many factors contributed to improve monitoring MPS in Tunisia during the last ten years of the study period, particularly the institution in 1987 of a metabolic bioclinic unit at La Rabta hospital in Tunis. The organisation of metabolic schools since 1988 further contributed to improve awareness of physicians about inborn metabolic disorders.

As reported previously in other populations, MPS I and III were the most frequent MPS types observed in this survey. The incidence of MPS I of approximately 1 in 165,000 live births is very similar to the estimates of Meikle in Australia and Baehner in Germany who estimated 1 in 111,000 and 145,000 live births, respectively(5,15). Although it was the most prevalent in this study, the crude rate of Sanfilippo disease (0.7 in 10,000,000 live births) was below the crude rate incidence of 1.37-1.89 per 100,000 live births reported in other locations (5-6,15,17). Perhaps this low incidence rate could be attributed to the fact that the mild somatic and skeletal features in this subtype don't attract the attention of Tunisian physicians. Type B seems to be more frequent than type A in Tunisia. The same distribution was supported in southern Europe, Brazil, Portugal, and in a large Turkish population living in Germany (8, 15, 18-19). Morquio disease, predominantly represented by the subtype A, had a crude incidence rate of 0.45 per 100,000 live births which was equivalent to that observed Germany (0.38), the Netherlands (0.22), and Australia (0.49)(5-6,15).

Morquio disease seems to be very frequent in Tunisia. Of the 36 cases when suspected MPS could not be confirmed, 21 were suspected to be type IV MPS. These figures indicate a predictable crude incidence of Morquio disease will be 1.23 (1/83,000 live births). MPS IV comprised 20% of the cases surveyed, which is much higher than the proportion of 8 to 13% reported in earlier surveys including a large series of MPS. Tunisian orthopaedists are more familiar with this disease than

paediatricians, since prominent skeletal features require often primarily orthopaedic advice. MPS type VI had higher incidence than was reported by Poorthuis et al. in Netherlands (0.15) and in Germany (0.23) where a high incidence of MPS VI was found in the Turkish population(6,15).

Patients with MPS type I were diagnosed at a later age (3.25 years; min-max: 0.58- 10 years) than patients with Hurler syndrome reported in the MPS I registry and for whom diagnosis was established before 2 years of age in 88% of cases (9). The mean age of diagnosis in Brazilian MPS type I, II and VI was 5-7 years and more than 7 years in MPS III and IVA (20). The mean age of diagnosis in patients collected by the Morquio A registry was 4.7 years, 67% of them were diagnosed before 5 years of age (10). Tunisian patients with Morquio disease were diagnosed at a mean age of 5.6 years.

Genotyping of MPS patients from several countries has disclosed variations in the frequency of specific mutations. In our investigation, among the five Tunisian families with MPS type I, P533 R was the most frequently mutation found; while W402 X and Q70X were the most frequent reported in European countries. The former was found in only one Tunisian family, with a severe Hurler phenotype (21-22). Molecular investigations of Morquio disease patients didn't identify the common mutations identified in the Caucasian or Turkish patients (23).

CONCLUSION

This survey demonstrated that MPS are frequent, but under-diagnosed in Tunisia. The high proportion of MPS diagnosed the last decade reflects a better awareness of clinicians about these disorders; however clinical assessments established the need for a greater dissemination of the appropriate assessments recommended for early monitoring and treatment of related MPS complications among health professionals.

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