A CLINICAL AND BIOCHEMICAL STUDY OF THE MUCOPOLYSACCHARIDOSES

H.S. NARAYANAN¹
K.S. MOHAN²
N. JAYASIMHA³
B.S. SRIDHARA RAMA RAO⁴

SUMMARY

Out of five thousand cases of mental retardation investigated over a period of ten years in NIMHANS, 80 cases were suspected to be cases of mucopolysaccharidoses. Out of these, 58 cases were confirmed as mucopolysaccharidoses after biochemical and radiological investigations. The different types of mucopolysaccharidoses were 40 cases of Hurler's, 14 of Hunter's and 4 of Morquio's syndrome. The special features of the cases are highlighted and the need for early diagnosis is emphasised.

Mucopolysaccharidoses (MPSes) refers to the group of disorders where a genetic deficiency leads to abnormal deposits of mucopolysaccharides in tissues and excretion of them in urine (Stanbury et al. 1972, 1983). The earliest cases of MPSes were reported in 1900 from Edinburgh by Thomp­son (Henderson 1940). In 1917, Hunter first reported two brothers whose clinical description was similar to the current description of the X-linked form of the disease. In 1919 Hurler described two unrelated boys with features exactly similar to the syndrome now associated with her name. Ellis et al. for the first time in 1936, introduced the term ‘Gargoylism’ due to an apparent resemblance of the patients to the gargoyles of certain cathedrals. Due to the unpleasant connotation for the families, this term is now given up. The term Hunter's syndrome is now reserved for the X-linked recessive variant while the Hurler's syndrome is used to indicate the autosomal variants. Brante (1952) and Meyer et al. (1959) identified the storage material as mucopolysaccharide (MPS). After the methods for elucidating the nature of MPS became available, several other types of MPSes were described. Based on the chemical defects and clinical features, McKusick classified them in a systematic manner (McKusick 1966). Each type is designated by the eponym and a roman numerical followed, where further subdivision is warranted, by a capital letter (Table 1).

The present paper reports observations made on cases of MPSes detected at this centre.

Material and Methods

Children seen at the MR clinic of NIMHANS formed the clinical material. A systematic screening of 5000 MR cases for metabolic defects during the period of 10 years led to the detection of 80 cases, which were clinically suspected to the MPSes. In all these cases systematic biochemical and radiological investigations were collected and processed for biochemical tests for detecting excretion of mucopolysaccharides. The biochemical methodology employed were both qualitative screening and

¹. Associate Professor of Psychiatry
². Resident in Psychiatry
³. Research Assistant in Neurochemistry
⁴. Professor and Head of the Department of Neurochemistry

National Institute of Mental Health & Neuro Sciences Bangalore - 560029, India.
A CLINICAL AND BIOCHEMICAL STUDY

Table 1
Tabulation of Mucopolysaccharidoses and Corresponding Primary Enzymatic Defects

| Eponym               | Designation     | Enzyme defect                      | Prevalance       |
|----------------------|-----------------|------------------------------------|-----------------|
| Hurler               | MPS - IH        | L-iduronidase                      | 1/1,00,000      |
| Scheie               | MPS - IS        |                                    | 1/ 50,000       |
| Hurler/Scheie        | MPS - IH/IS     |                                    | Rare            |
| Hunter               | MPS - II        | L-iduronosulphate sulphatase       | 1/1,50,000      |
| Sanfilippo-A         | MPS - IIIA      | Heparan-N-sulphatase               |                 |
| Sanfilippo-B         | MPS - IIIB      | Alpha-N-Acetyl glucosaminidase     |                 |
| Sanfillippo-C        | MPS - III C     | Alpha-glucosaminide-N-acetyl transferase |             |
| Morquio              | MPS - IV        | Galactose-6-sulphatase             | 1/1,00,000      |
| Maroteaux Lamy       | MPS - VI        | N-Acetyl galactosamine-4-sulphatase |                 |

quantitative confirmatory tests (McKusick 1966). The screening tests comprised of spot tests and turbidity tests, the confirmatory test done was cellulose acetate electrophoresis to determine the nature of the type of MPS excreted in urine, (Stanbury et al. 1983)

Results
The systematic screening of 80 clinically suspected cases led to the detection of 58 cases of MPSes. Based on the clinical, radiological, behavioural and biochemical findings of these 58 cases, following types were identified: Hurlers - 40, Hunter's - 14 and Morquios - 4.

The age and sex distribution of these are indicated in Table 2. The salient clinical features of individual type are indicated in Tables 3-5. The X-ray findings of the cases are indicated in Tables 6-8.

In all these cases, the biochemical screening procedures gave positive finding for the presence of MPS in urine. The screening procedures adopted mainly based on the appearance of metachromatic spots on the paper impregnated with tioluidine blue, turbidity developing with acid albumin or precipitation with cetyl pyrimidinium salt.

The confirmatory test was done to find out the specific excretion of MPS by carrying out cellulose acetate electrophoresis, using alcian blue staining technique. Depending upon the mobility of the specific MPS viz. heparan sulphate, dermatan sulphate, keratan sulphate, the differential diagnosis was made on the type and the amount of MPS. The Hurler's patients excreted both heparan and dermatan sulphate in the ratio of 2:1, whereas Hunter's type excreted equal amounts of dermatan and heparan sulphates. In the Morquio type the MPS excreted was keratan sulphate.

Discussion
During the present study identification was made of 40 cases of Hurler's, 14 cases of Hunter's and 4 cases of Morquio's. It was possible to arrive at the diagnosis by the clinical features and confirm the same by biochemical tests. In 20 out of the 40 Hurler's and in 12 out of 14 Hunter's and one of the Morquio, it was possible to examine the patients during followup atleast for a period of 3 years after their first visit, while the
Table 2
Age and Sex Distribution of Cases of MPSes

| Age Group (in years) | Hurler Male | Hurler Female | Hunter Male | Hunter Female | Morquio Male | Morquio Female | Total no. of cases Male | Female |
|----------------------|-------------|--------------|-------------|--------------|-------------|----------------|------------------------|--------|
| 0 - 3                | 14          | 6            | 1           | 0            | 0           | 0              | 15                     | 6      |
| 4 - 6                | 8           | 3            | 7           | 0            | 0           | 1              | 15                     | 4      |
| 7 - 9                | 6           | 2            | 2           | 0            | 1           | 0              | 9                      | 2      |
| 10 - 14              | 0           | 1            | 4           | 0            | 1           | 1              | 5                      | 2      |
| Total No. of cases   | 28          | 12           | 14          | 0            | 2           | 2              | 44                     | 14     |

Table 3
Clinical Features Seen in Hurler's Syndrome

| No. of cases |
|--------------|
| 1. Stunted growth | 28 |
| 2. Grotesque facies | 28 |
| 3. Protruberant abdomen | 28 |
| 4. Hyper teleorism | 28 |
| 5. Clouding of Cornea | 28 |
| 6. Hirsutism | 28 |
| 7. Hepatosplenomegaly | 26 |
| 8. Respiratory infection | 26 |
| 9. Dark bushy eye brows | 22 |
| 10. Depressed bridge of nose | 20 |
| 11. Kyphosis | 18 |
| 12. Scaphocephaly | 16 |
| 13. Peg like teeth | 10 |
| 14. Large mouth | 10 |
| 15. History of diarrhea | 10 |
| 16. Big hand | 8 |
| 17. Otitis | 6 |
| 18. Deafness | 5 |
| 19. Cardiovascular defects | 5 |

Table 4
Clinical Features Noted in Hunters

| No. of cases |
|--------------|
| 1. Stunted growth | 14 |
| 2. Grotesque facies | 14 |
| 3. Saddle shaped nose | 14 |
| 4. Wide mouth with peg shaped teeth | 14 |
| 5. Bushy eye brows | 14 |
| 6. Hepatosplenomegaly | 12 |
| 7. Hirsutism | 12 |
| 8. Broad ear | 9 |
| 9. Otitis | 9 |
| 10. Deafness | 6 |
| 11. Kyphosis | 4 |
| 12. Splenomegaly | 4 |
| 13. Restriction of joint movements | 1 |

Table 5
Clinical Features of Morquio's

| No. of cases |
|--------------|
| 1. Grotesque facies, bridge of nose depressed and short | 4 |
| 2. Protrusion of Jaw, Barrel shaped chest with Pectus Carinatum, Flat feet with genuvalgum, Dwarf and shortening of trunk | 2 |
| 3. Corneal clouding | 1 |

Table 6
Radiological Changes in Hurler's Syndrome

| Changes | No. of cases |
|---------|-------------|
| 1. Vertebral bodies-lower dorsal and upper lumbar wedge shaped, beaked-hook like | 38 |
| 2. Short thick phalangeal bones | 36 |
| 3. Skull-Hyperostosis | 30 |
| 4. Abnormally boot shaped sella turcica | 22 |
| 5. Ribs-Spinate | 20 |
| 6. Erosion of anterior clinoids | 16 |
| 7. Long bones-rarefaction and metaphyses spreading with upper spurring | 12 |

other cases did not come subsequently for followup. In the cases who came for followup, advice was given to seek medical consultation at the earliest sign of upper
there is no drug therapy for any of these cases, in countries abroad, parental detection and advocating medical termination of pregnancy is resorted to. However, such a facility is to be established in centers where adequate laboratory infrastructure is available and persons in charge have due respect for socioethical considerations.

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Table 7

Radiological Changes in Hunter’s Syndrome

| Changes                                      | No. of cases |
|---------------------------------------------|-------------|
| 1. Flattening of the condyle of mandible    | 13          |
| 2. Rounding of anterior surface of lower dorsal and lumbar vertebrae | 13          |
| 3. Thickening of Calvarium                  | 10          |
| 4. Beaking of lumbar vertebrae              | 6           |
| 5. Narrowing of acetabulum and of neck, shaft and angle of femur | 6           |
| 6. Deepening of sella and boot shaped sella turcica | 3           |

Table 8

Radiological Findings in Morquio’s Type

1. Skull was normal.
2. Long bones were coarse and trabeculated.
3. The lower end of radius and ulnar were irregular with cupping of distal epiphyseal plate of the ulna.
4. Metacarpals were short and stubby.
5. Lower end of femur and upper end of sibia showed irregular epiphyses with widening metaphyses.
6. Spinal transverse and articular processes were irregular with central “beaking” of lower thoracic and lumbar vertebrae.

respiratory tract infection. Many of the parents who ordinarily would not have taken serious note of, realised that in these cases there is an urgent need to minimise the respiratory tract infection. Although there is no drug therapy for cases of MPSes counselling the parents had a definite influence on the approach towards management of their children. It was also noted that none of the children had any behavioural disturbances.

With our experience, an early detection of MPSes would help in counselling the parents and advice them regarding the management of the cases. In view of the fact that