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**How to Distinguish Attenuated Forms of Mucopolysaccharidosis and Articular Forms of Juvenile Arthritis: Development of Diagnostic Algorithm Based on the Data from Multicenter Retrospective Study**

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***Background.*** *Differential diagnosis of attenuated forms of mucopolysaccharidosis (MPS) and juvenile idiopathic arthritis (JIA) can be challenging due to their similarities.* ***Objective. The aim of the study is to*** *create simple diagnostic criteria (DScore) that would allow to differentiate MPS from JIA for earlier MPS diagnosis.* ***Methods.*** *The retrospective multicenter study included analysis of clinical (joint, heart, eye involvement, hearing loss, hernias, psychomotor delay, noisy breathing, posture disorders, macrocephaly, hepatomegaly, splenomegaly, and growth delay) and laboratory data (ESR, CRP, hemoglobin, WBC, and platelets) from MPS patients (n=41) and from rheumatoid factor-negative polyarticular category of JIA patients (n=255). These variables allowed to differentiate both conditions and were used to create DScore.* ***Results.*** *Patients with MPS had younger onset age, male predominance, height and weight delay, lower inflammation markers (WBC, platelets, and ESR), and usually involved joints, especially cervical spine, upper limbs joints, hip, and small foot joints. The prevalence of eye involvement was similar for both diseases, however, the type of involvement was different. JIA patients had uveitis and its’ complications and MPS patients — corneal opacity and cataract. No differences in CRP levels were revealed in most cases. The major diagnostic criterion of MPS was the presence of more than one extra-articular manifestation associated with polyarticular involvement. DScore has included five following criteria: ESR ≤ 11 mm/h (38 points), height ≤ -2.0 SD (20 points), onset age of articular manifestations ≤ 1.1 year (24 points), male gender (15 points), and symmetrical limitation of movements in elbow joints (29 points). The sum > 38 points allowed us to differentiate MPS and JIA with sensitivity of 92.7% and specificity of 91.0%.* ***Conclusion.*** *This DScore can be used for differential diagnosis of mild MPS and JIA alongside with routine diagnostic procedures. DScore allows us to identify a group of patients with joint involvement who require MPS exclusion.*

***Keywords:*** *mucopolysaccharidosis, juvenile idiopathic arthritis, arthropathy, diagnostic criteria*

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Patients with MPS (n=165)

Severe forms of MPS

Patients with attenuated forms of MPS (n=41)

Patients with all forms of JIA (n=753)

Patients with systemic, oligoarthritis, rheumatoid factor-positive polyarticular arthritis, enthesitis-related arthritis, psoriatic arthritis, arthritis associated with IBD, undifferentiated arthritis

Patients with rheumatoid factor-negative polyarticular JIA with or without uveitis (n=255)

**Fig. 1.** Study sampling

*Note.* RF (РФ) — rheumatoid factor; IBD (ВЗК) — inflammatory bowel disease; JIA (ЮИА) — juvenile idiopathic arthritis.

**Table 1.** Systemic (extra-articular) manifestations in patients with attenuated forms of MPS

at the disease onset and at the time of diagnosis

|  |  |  |
| --- | --- | --- |
| **Symptoms** | **Frequency of symptoms at the disease onset, *n* (%)** | **Frequency of symptoms at the time of diagnosis, *n* (%)** |
| Age, years, *Me* (25%; 75%) | 2,0 (0,6; 3,0) | 7,6 (4,6; 11,9) |
| Eyes involvement, *n* (%) | 8 (19,5) | 25 (61,0) |
| Heart involvement:* valve alterations, *n* (%)
* cardiomyopathy, *n* (%)
 | 5 (12,2)–– | 35 (85,4)34 (83,0)17 (41,5) |
| Rhinitis/otitis, *n* (%) | 12 (29,3) | 29 (70,7) |
| Mild Gurler phenotype, *n* (%)  | 8 (19,5) | 34 (82,9) |
| Hepatosplenomegaly, *n* (%)  | 18 (43,9) | 7 (17,1) |
| Splenomegaly, *n* (%) | – | 7 (17,1) |
| Hepatomegaly | – | 20 (48,8) |
| Macrocephaly, *n* (%) | – | 24 (58,5) |
| Short neck, *n* (%) | – | 27 (65,9) |
| Noisy breathing, *n* (%) | – | 9 (22,0) |
| Spine and chest deformity, *n* (%) | 18 (43,9) | 23 (56,1) |
| Posture problems, *n* (%) | – | 35 (85,4) |
| Hip dysplasia, *n* (%) | – | 17 (41,5) |
| Hearing loss, *n* (%) | 0 | 18 (43,9) |
| Hernias, *n* (%) | 12 (29,3) | 22 (53,7) |
| Joint involvement at onset | 24 (58,5) | – |
| Involvement of hand joints at onset | 19 (46,3) | – |
| JIA diagnosis at onset | 8 (19,5) | – |

*Note.* JIA (ЮИА) — juvenile idiopathic arthritis.

**Table 2.** Comparison of polyarticular forms of JIA and attenuated forms of MPS

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicator** | **MPS (*n* = 41)** | **JIA (*n* = 255)** | ***p*** |
| **Demography** |  |  |  |
| Onset age, years, *Me* (25%; 75%) | 1,0 (0,6; 3,0) | 4,7 (2,1; 8,8) | 0,0000001 |
| Gender, females, *n* (%) | 16 (39,0) | 186 (72,9) | 0,00002 |
| **Anthropometry** |  |  |  |
| Height, SD, *Me* (25%; 75%) | −1,0 (−3,1; −0,6) | 0,0 (−0,9; −0,8) | 0,001 |
| Weight, SD, *Me* (25%; 75%) | −0,65 (−2,5; 0,3) | 0,19 (−0,6; 1,0) | 0,005 |
| BMI, %, *Me* (25%; 75%) | 107,6 (98,8; 113,9) | 50,7 (20,4; 80,5) | 0,0000001 |
| BMI, SD, *Me* (25%; 75%) | 1,0 (0,0; −2,0) | 0,0 (−0,9; 0,8) | 0,004 |
| **Inflammatory activity** |  |  |  |
| ESR, mm/h, *Me* (25%; 75%) | 6,0 (3,0; 8,0) | 8,0 (4,0; 19,0) | 0,030 |
| CRP, mg/l, *Me* (25%; 75%) | 1,4 (0,0; 3,2) | 1,5 (0,0; 6,6) | 0,120 |
| WBC × 109/l, *Me* (25%; 75%) | 6,1 (5,3; 7,7) | 7,2 (6,0; 9,1) | 0,018 |
| Platelets × 109/l, *Me* (25%; 75%) | 228 (1970; 293) | 328 (275; 400) | 0.0000001 |
| Hemoglobin, g/l, *Me* (25%; 75%) | 129 (121; 138) | 123 (116; 130) | 0.0000001 |
| **Joint involvement** |  |  |  |
| Involved joints, *Me* (25%; 75%) | 39,0 (10,0; 42,0) | 11,0 (7,0; 18,0) | 0,0000001 |
| Cervical spine, *n* (%) | 15 (36,6) | 48 (18,8) | 0,01 |
| Temporomandibular, *n* (%) | 0 (0) | 24 (9,4) | 0,108 |
| Sternoclavicular, *n* (%) | 0 (0,0) | 6 (2,4) | 0,44 |
| Shoulder, *n* (%) | 28 (68,3) | 27 (10,6) | 0,000001 |
| Elbow, *n* (%) | 37 (90,2) | 60 (23,6) | 0,000001 |
| Wrist, *n* (%) | 34 (82,9) | 114 (44,7) | 0,000006 |
| Metacarpophalangeal, *n* (%) | 30 (73,2) | 114 (44,7) | 0,0007 |
| Proximal interphalangeal, *n* (%) | 30 (73,2) | 125 (49,0) | 0,004 |
| Distal interphalangeal, *n* (%) | 30 (73,2) | 41 (16,1) | 0,0000001 |
| Hip, *n* (%) | 24 (58,5) | 49 (19,2) | 0,0000001 |
| Hip osteoarthritis, *n* (%) | 8/24 (32,0) | 13/49 (26,5) | 0,620 |
| Sacroiliac, *n* (%) | 0 (0) | 7 (2,8) | 0,283 |
| Knee, *n* (%) | 37 (90,2) | 200 (78,4) | 0,088 |
| Ankle, *n* (%) | 19/25 (76,0) | 167 (65,5) | 0,288 |
| Subtalar, *n* (%) | 0/25 (0) | 38 (14,9) | 0,038 |
| Metatarsal, *n* (%) | 0/25 (0) | 26 (10,2) | 0,094 |
| Metatarsophalangeal joints, *n* (%) | 10/25 (40,0) | 53 (20,8) | 0,028 |
| Toe joints, *n* (%) | 10/25 (40,0) | 51 (20,0) | 0,021 |
| **Extra-articular features** |  |  |  |
| Eyes involvement at onset, *n* (%) | 7 (17,1) | 32 (12,6) | 0,432 |
| Systemic features score, *Me* (25%; 75%) | 5 (4; 7) | 0 (0; 0) | 0,0000001 |

*Note.* MPS (МПС) — mucopolysaccharidosis; JIA (ЮИА) — juvenile idiopathic arthritis. BMI (ИМТ) — body mass index; ESR (СОЭ) — erythrocyte sedimentation rate; CRP (СРБ) — C-reactive protein. SD — standard deviation; *Me* — median.

**Table 3.** Sensitivity, specificity, and OR values of criteria for differentiating of attenuated forms of MPS and polyarticular JIA \*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicator** | **Se** | **Sp** | **OR (95% CI)** | ***р*** |
| **Demography** |  |  |  |  |
| Males | 61,0 | 72,9 | 4,2 (2,1; 8,4) | 0,000015 |
| Onset age ≤ 1 year | 56,7 | 95,7 | 28,2 (10,5; 76,3) | 0,000001 |
| **Anthropometry** |  |  |  |  |
| Height ≤ −2,0 SD | 45,2 | 95,4 | 17,2 (6,3; 46,8) | 0,0000001 |
| Weight ≤ −1,0 SD | 48,4 | 85,2 | 5,4 (2,2; 13,0) | 0,00008 |
| BMI ≥ 1 SD | 61,3 | 78,9 | 2,7 (1,1; 6,3) | 0,000004 |
| **Laboratory data:** ESR ≤ 11 mm/h | 96,6 | 38,5 | 182 (22,2; 1490,5) | 0,0000001 |
| **Joint involvement** |  |  |  |  |
| Cervical spine | 36,6 | 81,2 | 2,5 (1,2; 5,1) | 0,01 |
| Shoulder | 70,0 | 89,4 | 19,7 (9,0; 43,2) | 0,000001 |
| Elbow | 90,2 | 76,4 | 29,9 (10,2; 87,3) | 0,000001 |
| Wrist | 90,2 | 55,3 | 6,0 (2,6; 14,1) | 0,000006 |
| Metacarpophalangeal | 73,2 | 55,3 | 2,8 (1,4; 5,9) | 0,0007 |
| Proximal interphalangeal | 73,2 | 51,0 | 2,8 (1,4; 5,9) | 0,004 |
| Distal interphalangeal | 73,2 | 83,9 | 14,2 (6,6; 30,7) | 0,0000001 |
| Hip | 58,5 | 80,8 | 5,9 (3,0; 11,9) | 0,0000001 |
| Talocalcaneal | - | 85,1 | 5,9 (3,0; 11,9) | 0,038 |
| Metatarsophalangeal | 40,0 | 79,2 | 2,5 (1,1; 6,0) | 0,028 |
| Toe joints | 40,0 | 80,0 | 2,7 (1,1; 6,3) | 0,021 |
| Number of affected joints > 33 | 100 | 100 | – | – |
| **Extra-articular features** |  |  |  |  |
| Systemic features, yes | 100 | 87,5 | – | 0,00000 |
| Number of systemic features > 1 | 95,1 | 100 | – | 0,000001 |
| Eyes involvement | 17,4 | 87,4 | 1,4 (0,6; 3,5) | 0,434 |

*Note.* <\*> — at the time of MPS diagnosis.ESR (СОЭ) — erythrocyte sedimentation rate. Se — sensitivity, SD — standard deviation, Sp — specifity, OR (ОШ) — odds ratio, 95% CI (ДИ) — 95% confidence interval.

**Table 4.** Criteria included in the development of the diagnostic model and DScore calculation

|  |  |
| --- | --- |
| **Major criteria** | **Polyarticular involvement and more than 1 extra-articular manifestation** |
| **Minor criteria** | Β | SE | P |  | Points (scoring criteria) \* |
| ESR ≤ 11 mm/h | 0,38 | 0,07 | 0,000002 | ESR | 38 (≤ 11 mm/h) or 0 (> 11 mm/h) |
| Height ≤ −2,0 SD | 0,20 | 0,07 | 0,003 | РоHeightст | 20 (≤ −2,0 SD) or 0 (> −2,0 SD) |
| Onset age ≤ 1.0 year | 0,24 | 0,08 | 0,002 | Onset age | 24 (≤ 1.0 year) or 0 ( > 1.0 years) |
| Male gender | 0,15 | 0,06 | 0,015 | Gender | 15 (males) or 0 (females) |
| Symmetric elbows involvement | 0,29 | 0,07 | 0,00003 | Symmetric elbow involvement | 29 (yes) or 0 (no) |

*Note.* Differentiation of attenuated forms of MPS and JIA requires major criterion or sum of minor criteria > 38 points. <\*> — DScore cut-off > 38 points for minor criteria sum.

**Fig. 2.** ROC-analysis for the diagnosis of attenuated forms of MPS in children via DScore calculated with the developed dataset

*Note.* The threshold value that gave the maximal sensitivity and specificity was selected as the optimal cut-off. Area under the curve (AUC) = 0,977 (95% CI 0,953; 0,991) and DScore for MPS > 38 points with the sensitivity of 92.7% and the specificity of 91.0%.

**RESEARCH LIMITATIONS**

The study was limited by its retrospective design and the lack of some data in medical records. Rheumatologists do not always provide the information on some phenotypic signs (such as facial dysmorphy, short neck, kyphosis, or hernias), or internal organ involvement (heart, liver, and spleen ultrasound is not mandatory for nonsystemic JIA forms). While specialists in metabolic diseases do not always detail joint lesions. The rheumatologist examination is mandatory in the management of a patient with JIA. It is reflected in the calculation of extra-articular manifestations number. Altogether it could affect the study results.

**FINANCING SOURCE**

Not specified.

**DISCLOSURE OF INTEREST**

Not declared.