Clinical and genetic evaluation of DMA Dysmorphies in patients with profound mental retardation

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Summary

Prior categorizations of mental retardation, defined solely by IQ, have largely been abandoned in favor of an approach that looks at how much support the retarded person needs in various areas of his or her life at any given time. [1] There are several hundred possible causes of mental retardation. They include genetic conditions characterized by mild to severe mental retardation, slow physical development, and characteristic physical features. [2]
Our study proposes to identify the major phenotypic aspects of cranio-facial and DMA in two patients with profound mental retardation.
Material and method. We have studied a lot of 128 patients, selected from a group of 436 mentally retarded patients, which had the family agreement. The patients were hospitalized in 3 mental institutions of Constanta. In these cases we emphasized the major features of DMA provides important insight into understanding the genotype-phenotype correlation in plurimalformative syndrome in patients with profound mental retardation. In addition, the patient was investigated by genetic analyses.
Results and conclusion. Although the cranial-facial aspects were severe, the caryotype analysis performed by G mark showed that the two patients have normal caryotype, which mean that the genetic factor is not always responsible of the dysmorphic aspects of DMA.
Genetic investigations were made in collaboration with Department of Medical Genetics of the Faculty of Medicine, "Ovidius" University of Constanta.

Keywords: plurimalformative syndrome, DMA phenotype, profound mental retard.

Introduction

Mental retardation, below average level of intellectual functioning, is usually defined by an IQ below 70-75, combined with limitations in the skills necessary for daily living. [3] Daily living skills include aptitudes as communication, the ability to care for oneself, and the ability to work. [4]

The definition of mental retardation has evolved over the years. Prior categorizations of mental retardation, defined solely by IQ, have largely been abandoned in favor of an approach that evidences the degree of support the retarded person needs in various areas of his/her life at any given time. [1]

There are several hundreds possible causes of mental retardation. They include genetic conditions characterized by mild to severe mental retardation, slow physical development, and characteristic physical features. [2]

About 75-80 percent of is familial (runs in families), and 20-25 percent is due to

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organic problems, such as chromosomal abnormalities or brain damage [5,6]. Mild to severe mental retardation is a symptom of several hundred single-gene disorders and many chromosomal abnormalities, including small deletions. [7] Based on twin studies, moderate to severe mental retardation does not appear to be familial, but mild mental retardation does. [8] That is, the relatives of the moderate to severely mentally retarded evidence normal IQ ranges, whereas the families of the mildly mentally retarded have IQs skewing lower. [9]

It is generally accepted that intelligence is related to both heredity and environment. [10] Studies done on families, particularly among identical twins and adopted children, have shown that heredity is an important factor in determining intelligence; but they have also suggested that environment is a critical factor in determining the extent of its expression. [11] For instance, children reared in orphanages or other environments that are comparatively unstimulating tend to show retarded intellectual development. [12] In recent years, controversy regarding intelligence has centered primarily on how much of each factor, heredity and environment, is responsible for an individual's level of intelligence. [13]

The following ranges, based on the (WAIS), are in standard use today: [14] *(Table 1)*. Cranial-facial and dentomaxillary dysmorphies are growth and shape deficiencies of DMA and refer to lop-sided ratio between them, establishing severe functional deficiencies involving mastication, breathing, swallowing, phonation and mimicry. Dysmorphogeneses are specific morbid entities and their etiology is based on genetic factors and neuron-hormonal regulatory system. [15].

The plurimalformative syndrome is a multisystemic disease. The etiology is unknown. [16] In the following cases, although the dentomaxillary anomalies and the cranial-facial dysmorphogeneses are

Table 1.Wechsler Adult Intelligence Scale (WAIS)

Class	IQ
Profound mental retardation	Below 20
Severe mental retardation	20-34
Moderate mental retardation	35-49
Mild mental retardation	50-69
Borderline deficiency	70-79

severe, it seems that the genetic factor is less implicated, because the caryotype analysis performed by G mark proved normal.

Mild to severe mental retardation is a symptom of several hundred single-gene disorders and many chromosomal abnormalities, including small deletions. [17] Based on twin studies, moderate to severe mental retardation does not appear to be familial, but mild mental retardation does. That is, the relatives of the moderate to severely mentally retarded evidence normal ranges of IQs, whereas the families of the mildly mentally retarded have IQs skewing lower. [18]

Heritability, as used professionally in genetics, has a very precise definition. It is that proportion of the observed variation in a particular phenotype within a particular population (and, in practice, in a particular study), that can be attributed to the contribution of genotype (inheritance). [19]

Objective

Our study proposes to identify the major phenotypic cranio-facial and DMA aspects in two patients with profound mental retardation and if there is any interdependence between the severity of these signs and genetic factors.

Method

We have studied a batch of 128 patients, selected from a group of 436 mentally

retarded patients who had the family agreement. The patients were hospitalized in 3 mental institutions and a special school in Constanta. Special investigation charts, presented below, were devised for all 128 patients. Step 1: establishing the mental retarded study of the patients; step 2: establishing the constitutional type, anthropologic, morphologic figure type and the antropometric facial type; step 3: assessment of somatic growth; step 4: assessment of cephalometry; step 5: assessment of facial sizes; step 6: clinical study of cranial-facial dysmorphies; step 7: examination of the dental-maxillary phenotype.

Genetic investigations were made for 28 patients with cranial-facial and dental-maxillary severe dysmorphies: family investigations, caryotype analysis performed by Fish technique and G mark and other investigations along with the Department of Medical genetics of the Faculty of Medicine, "Ovidius" University Constanta.

Results

Case 1

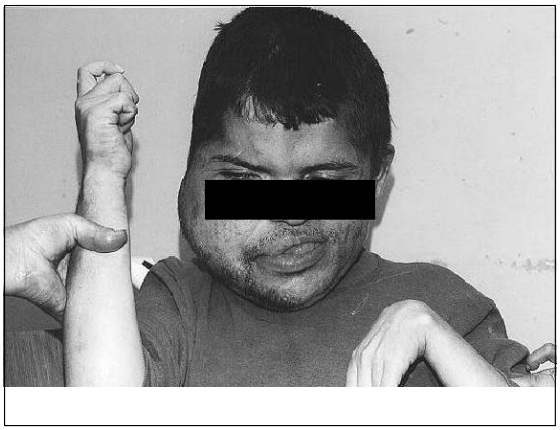
Patient S.N., Age: 27, Sex: M, IQ<20 (profound mental retardation)

The patient is hospitalized in the Negru Voda recuperation center for patients with neuro-psychiatric handicap. There was no available information about his family. From his chart and our investigations we present the following clinic aspects:

S.N. Cranial-facial Phenotype (*Figure 1*)

- ⌘ flat occiput;
- ⌘ high, prominent forehead;
- ⌘ short, thickly neck;
- ⌘ hemifacial hypertrophy with consecutive facial asymmetry;
- ⌘ thin, low set eyebrows;
- ⌘ short nose, deviated on the healthy side;
- ⌘ eyes asymmetry with refraction problems (ambliopy);

Figure 1. S.N., Cranial-facial phenotype



- ⌘ small ears comparing with the head size;
- ⌘ big, asymmetric mouth permanently open;
- ⌘ thick lips;
- ⌘ macroglossia with tongue protrusion;
- ⌘ hypertonus of the tongue;
- ⌘ deviation of menton on the healthy side;
- ⌘ very short neck.

S.N. Dental-maxillary Phenotype (*Figures 2, 3*)

- ⌘ crowding dental-alveolar disharmony (angle II/1);
- ⌘ asymmetric maxillary dental-alveolar arch;
- ⌘ persistence of deciduous tooth (62);
- ⌘ 23 embedded;
- ⌘ supernumerary maxillary premolar;
- ⌘ enamel hypoplasia in 24, 44, 45, 34, 35;
- ⌘ deep asymmetric palatal arch;
- ⌘ deep chronic marginal periodontitis localized in 25, 26, II-III degree dental mobility;
- ⌘ superficial chronic marginal periodontitis;
- ⌘ macroglossia;
- ⌘ geographic tongue;
- ⌘ chronic moniliasis;
- ⌘ spontaneous gingival bleeding.

Figure 2. S.N., Dental-maxillary phenotype on the left side

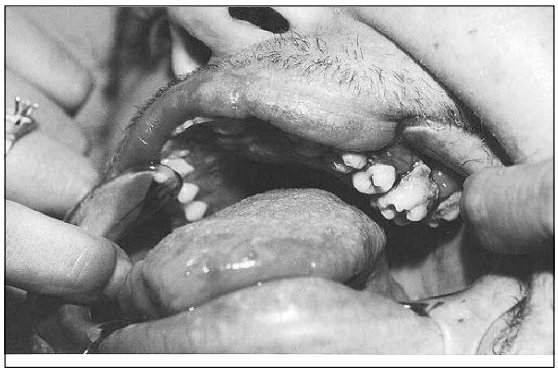


Figure 3. S.N., Dental-maxillary phenotype on the right side

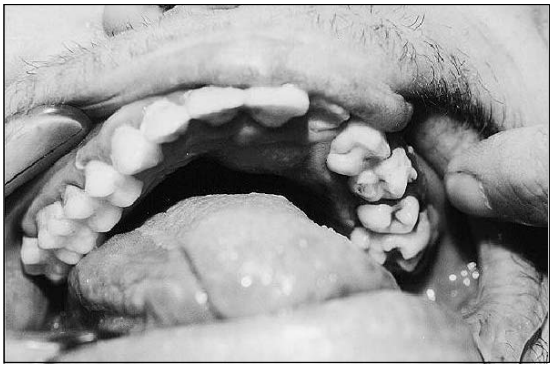


Figure 4. Pectus escavatus

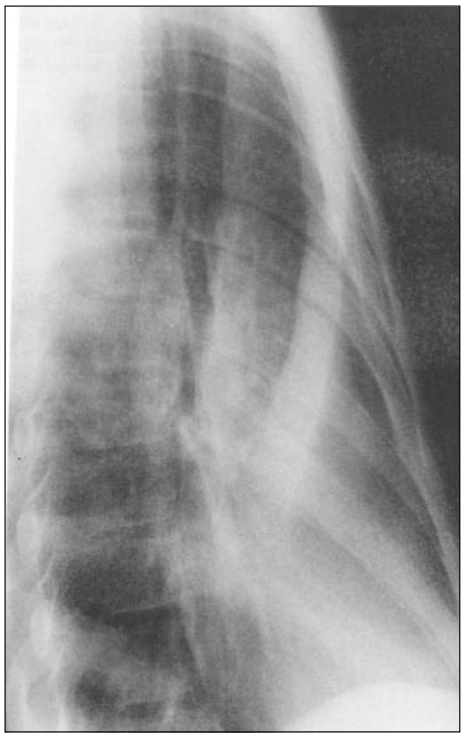
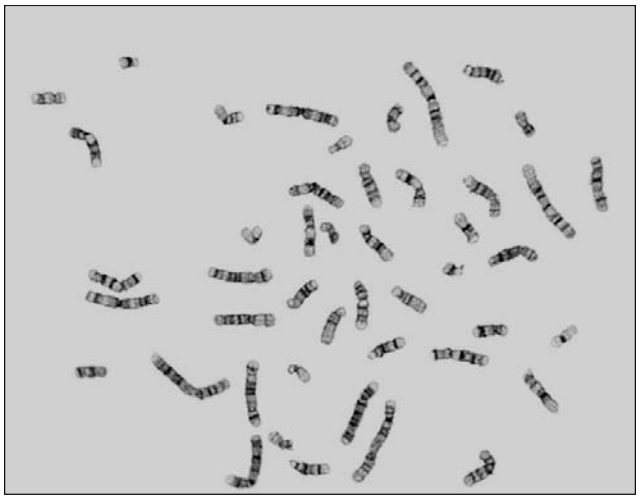


Figure 5. Caryotype analysis performed by G mark showed a normal caryotype: 46, XY



Complementary examinations: TA 90/60 mm Hg, pulse 68/min, ultrasound test: normal liver parenchyma, polycystic right kidney.

Radiological examination: Pectus escavatus (*Figure 4*), trunk profile: severe depression of the distal extremity of the stern.

Caryotype analysis performed by G mark showed a normal caryotype: 46, XY (*Figure 5*)

Case 2

Patient D.V., Age: 22, Sex: F, IQ<20 (profound mental retardation)

The patient is hospitalized in Techirghiol Psychiatric Hospital. She has a severe physic and mental handicap, which requires permanent assistance, the patient being incapable of taking care of herself. The results of anthropometric measurements and data from her chart are:

D.V. Cranio-facial phenotype (*Figure 6*)

⌘ microcephaly;
⌘ anterior-posterior flatted head;
⌘ flat occiput;
⌘ broad, prominent forehead;
⌘ short neck;
⌘ small ears, low set and anterior rotation;
⌘ hypertelorism;
⌘ exoftalmy;
⌘ divergent strabism;
⌘ low set eyebrows, unusual flare, extension to midline;
⌘ exaggerate hairy forehead;
⌘ short, swollen nose.

D.V. Dental-maxillary Phenotype (*Figure 7*)

⌘ maxillary proalveolary denture;
⌘ shape asymmetry of dental arches;
⌘ shape and position teeth anomalies;
⌘ generalized severe chronic marginal periodontitis, dental mobility III, IV, great deposits of supra- and subgingival tartar between teeth;
⌘ enamel hypoplasia;
⌘ severe lack of poise occlusal-articulary;
⌘ macroglossia.

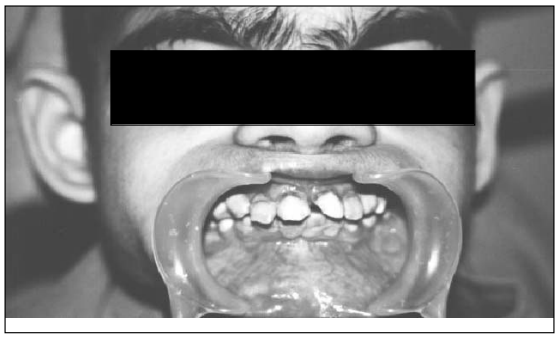
Complementary examinations: TA 11/60 mm Hg; pulse 65/min; radiological exam: congenital scoliosis (*Figure 8*); vertebral defect, as part of generalized bone disorder.

Genetic examination:

Family investigation: the patient was deserted in the hospital maternity and then transferred to a home. At the age of 7 she was transferred to the Techirghiol Psychiatric Hospital, where she is still in charge. In her chart there is no information available about her family.

Caryotype analysis performed by G mark evidenced normal caryotype: 46, XX (*Figure 9*).

Figure 6. D.V., Cranio-facial phenotype



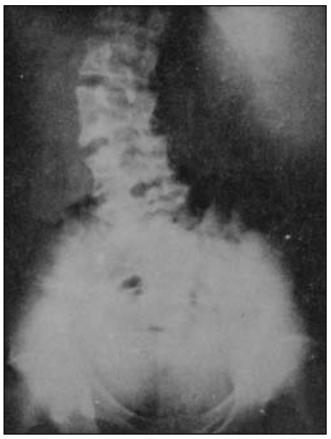


Figure 8. Congenital scoliosis, vertebral defect

Figure 7. D.V., Dental-maxillary phenotype

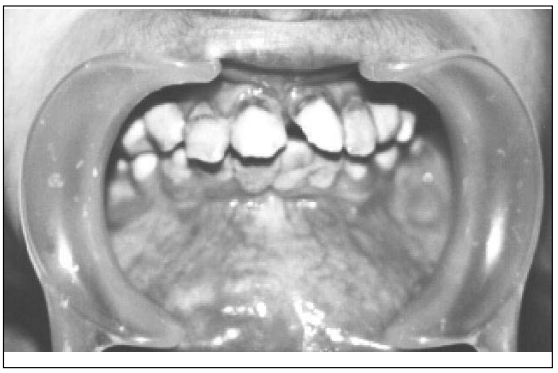
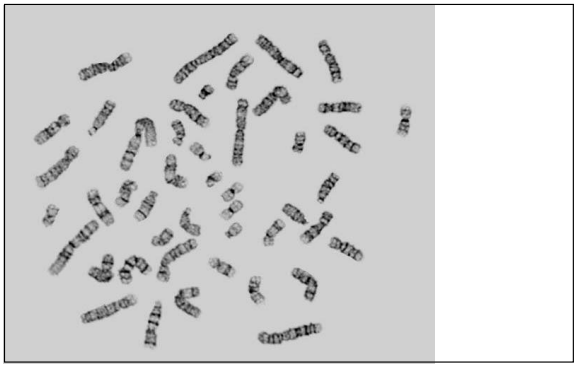


Figure 9. Caryotype analysis performed by G mark showed a normal caryotype: 46, XX



Discussion

The term mental retardation has gradually acquired pejorative and shameful connotations over the last few decades. In North America, the term developmental delay has become an increasingly preferred synonym among parents and physicians, but in other contexts as well. Elsewhere however, developmental delay is generally used to imply that appropriate intervention will improve the condition, allowing for catching up, that is, the individual's current difficulties can be temporary.

Developmental disability is also preferred by most, but can also refer to other physical or psychiatric disabilities. [20] Intellectual disability is occasionally used as a synonym for the same reasons but also lacks specificity as it also applies to dementing conditions such as syndrome. The American Association on Mental Retardation continues to use the term mental retardation.

Comparative analysis of cranial-facial and dental-maxillary phenotype of the two patients showed that they have many organic malformations and DMA dysmorphy is similar. (*Table 2*)

Table 2. Comparative study of cranio-facial and DMA dysmorphy for the two patients with severe mental retard

Phenotype	Patient S.N.	Patient D.V.
Cranial Phenotype	Macrocephaly; Tower head; Flat occiput; High, prominent forehead	Microcephaly with brachycephaly; Flat occiput; Broad, prominent forehead; Anterior-posterior flatted head
	Short, thickly neck	Short neck
Facial Phenotype	Hemifacial hypertrophy with consecutive facial asymmetry; Thin, low set eyebrows; Short nose, deviated on the healthy side; Eyes asymmetry with refraction problems(ambliopy); Small ears comparing with the head size; Big, asymmetric mouth permanently open; Thick lips; Macroglossia with tongue protrusion; Hypertonus of the tongue; Deviation of menton on the healthy side	Hypertelorism; Exoftalmy; Divergent strabism; Low set eyebrows, unusual flare, extension to midline; Exaggerate hairy forehead; Short, swollen nose; Long lashes
Dento-maxillary Phenotype	Crowding dental-alveolar disharmony (Angle II/1); Asymmetric maxillary dental-alveolar arch; Persistence of deciduous tooth (62); 23 embedded; Supernumerary maxillary premolar; Enamel hypoplasia at 24, 44, 45, 34, 35; Deep asymmetric palatal arch; Deep chronic marginal periodontitis localized at 25, 26, dental mobility II, III; Superficial chronic marginal periodontitis; Macroglossia; Geographic tongue; Chronic moniliasis; Spontaneous gingival bleeding with tongue protrusion	Maxillary proalveolary denture; Shape asymmetry of dental arches; Shape and position of teeth anomalies; Generalized severe chronic marginal periodontitis, dental mobility III, IV, great amounts of supra - and under gingival tartar between all teeth; Enamel hypoplasia; Severe lack of poise occlusal - articulary Macroglossia

Heritability, as used professionally in genetics, has a very precise definition. It is that proportion of the observed variation in a particular phenotype within a particular population (and, in practice, in a particular study), that can be attributed to the contribution of genotype (inheritance). [21]

Conclusion

1. Comparative analysis of cranial-facial and dental-maxillary phenotype of the two patients reveals that both of them display the same dysmorphic aspects such as: flat occiput, prominent forehead, short neck, low set eyebrows, asymmetric dental-alveolar arch, severe chronic marginal periodontitis, dental mobility, enamel hypoplasia, macroglossia.

2. Although the cranial-facial dysmorphic aspects of S.N. are more numerous and more severe, for S.N., dental-maxillary dysmorphies are more severe in the second case, meaning that in these cases, there is no certain concordance between the gravity of the cranial-facial dysmorphy and dysmorphic aspects of DMA.

3. Based on clinical aspects and the results obtained by analyzing the caryotype performed by G mark, the two patients having normal caryotype (46XY; 46XX), the diagnosis of plurimalformative syndrome with normal caryotype was made.

4. Although the cranial-facial aspects were severe, the caryotype analysis performed by G mark showed that the two patients have normal caryotype, which means that the genetic factor is not always responsible for the dysmorphic aspects of DMA.

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