SIGNIFICANCE OF MORPHOGENETIC INFORMATIVE VARIANTS IN GENETIC EVALUATION OF MENTAL RETARDATION

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Abstract. We evaluated the presence or absence of informative morphogenetic variants in cases with mental retardation compared with mentally healthy subjects. Cases diagnosed with mental retardation were matched by age and sex with control subjects and examined for the presence of informative morphogenetic variants. The aim of the study was to investigate their prevalence and mean number in these subjects. Mentally healthy individuals showed a lower mean score than those mentally retarded. A higher mean number was also noticed in cases with idiopathic and in those with severe mental retardation. The increased number of anomalies in these cases suggests that such congenital markers could indicate a prenatal onset of the mental deficit.

Keywords: informative morphogenetic variants, mental retardation, genetic evaluation

INTRODUCTION

Mental retardation is defined as a developmental disability characterized by lower intelligence and limited daily living skills. It is estimated that the condition is present in 2-3% of the population, either isolated or part of a syndrome. Mental retardation may occur due to many causes, including genetic and environmental ones. There may be prenatal causes such as congenital infections, prolonged maternal fever in the first trimester; exposure to different drugs or to alcohol, untreated maternal phenylketonuria. Other causes are single-gene disorders that result in mental retardation and many of them are associated with dysmorphic features. It was estimated that about 25% of cases with mental retardation have a chromosome abnormality [4]. Mental retardation may also occur due to perinatal or postnatal causes. Retrospective allocation of the cause of mental retardation can be very difficult in some cases. In almost half of the cases physicians are unable to determine the etiology. It would be useful to identify a marker that might indicate an association with a prenatal event, such as informative morphogenetic variants. These are defects that in themselves do not have medical importance and they may occur in healthy subjects aswell. They suggest an altered morphogenesis and alert the clinician to the possibility of a more severe morphological or functional defect. Diagnosis of mental terardation depends on a comprehensive medical history, a complete physical examination and a careful developmental assessment of the case [1]. Mental retardation in young children is often missed by clinicians. The most common reasons for delayed diagnosis include believing that normal appearance and ambulation are not compatible with mental retardation or assuming that testing is not possible in young children.

Congenital defects are defects present at birth and may occur due to genetic causes, such as genic or chromosomal abnormalities, may be due to environmental agents that interfere normal embryogenesis or may have a multifactorial etiology [8, 13]. They have been divided into major and minor anomalies. Major anomalies have adverse effects on the individual's health, functioning or social acceptability. The minor ones are generally considered of limited medical significance, but they represent valuable indicators of disturbance in early neurodevelopment. Several studies have demonstrated relationships between multiple minor anomalies or morphogenetic informative variants and mental retardation, autism, epilepsy, hyperactivity or schizophrenia [2, 11, 12].

MATERIALS AND METHODS

The authors evaluated the presence or absence of informative morphogenetic variants (IMV) in cases with mental retardation compared with mentally healthy subjects. The aim of the study was to investigate the prevalence and the mean number of informative morphogenetic variants in these two groups, together with correlations with the history of the cases.

The incidence and the mean number of informative morphogenetic variants were investigated in 242 cases hospitalized in the Neuropsychiatry Center for Children and Teenagers from Timisoara. Data were collected by performing multiple physical examinations and measurements where necessary for a greater accuracy. From the examined group, 82 children had an association between informative morphogenetic variants and mental retardation. 40 of them were girls and 42 were boys. Their age varied between 1 year and 16 years.

Considering the probable etiology of mental retardation cases were divided in:

- Chromosomal disorders - 8 cases
- Single gene disorders - 9 cases
- Peri and postnatal lesions due to environmental agents - 3 cases
- Unknown etiology - 62 cases

Cases diagnosed with mental retardation were matched by age and sex with control subjects and examined for the presence of morphogenetic informative variants (Table 1). Healthy subjects were chosen randomly from nursery schools, kindergartens, schools and highschools. Frequency and mean value for these minor anomalies were calculated.

The clinical genetics evaluation used a standard data set for the collection of historical data, including prenatal, teratogen exposure, perinatal, developmental, language, health and family history. Neurological and physical examinations were performed. Paraclinical investigations included electroencephalographies and karyotyping.

Table 1. Informative morphogenetic variants

Face	Synophris, anteverted nostrils, bifid tip of nose, high arched palate, bifid uvula, micrognatia,
Eyes	Epicanthic folds, upslanting palpebral fissures, downslanting palpebral fissures, short palpebral fissures, hypertelorism, hypotelorism
Ears	Malformed ears, asymmetric ears, low set ears, small ears, preauricular pits or tags, ear lobe creases
Head and Neck	Webbed neck, flat occiput, prominent occiput
Hair	Two or more parietal whorls, abnormal posterior whorl
Hands	Clinodactily, partial cutaneous syndactily, simian crease, Sydney crease
Trunk	Accessory nipples, short stern, haemangioma, cafe-au-lait spots, acromial dimples
Feet	Broad hallux, wide distance between toes 1 and 2, partial syndactily, prominent heel

RESULTS

Subjects with mental retardation had significantly more informative morphogenetic variants than comparison subjects. Mentally healthy individuals showed a low mean score of morphogenetic informative variants. More than 50% of mentally retarded cases had more than 3 informative morphogenetic variants (Fig. 1). The anomalies prevailed in the craniofacial region.

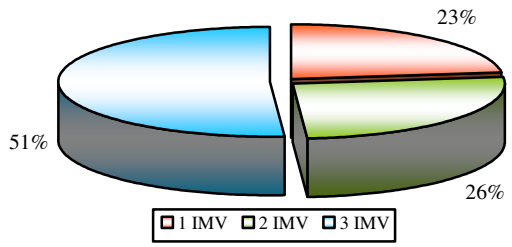

Figure 1. Incidence of informative morphogenetic variants in mentally retarded cases

Expressing the mean values as informative morphogenetic variants per case, the figures were 2.48 in mentally retarded cases and 1.05 in the control group, difference that is statistically very significant ($p<0.001$). The number of informative morphogenetic variants was higher in the subgroup of mentally retarded subjects in whom a genetic etiology was considered. The number was also higher in the subgroup with mental retardation of unknown etiology. The majority of cases from the subgroup with exogeneous etiology had only 1 informative morphogenetic variant.

The mean value of informative morphogenetic variants per case was the highest in those with chromosomal disorders and significantly lower in those with mental disability due to environmental agents (Table 2).

According to the severity of mental retardation, cases were divided in three groups:

- A group with mild retardation (46 cases = 56.09%)
- A group with moderate retardation (25 cases = 30.48%)
- A group with severe retardation (11 cases = 13.41%)

Significantly higher figures were obtained for the mean number of informative morphogenetic variants in the group with severe mental retardation (5.09 informative morphogenetic variants/case), statistically very significant ($p<0.001$) and in the group with moderate mental retardation (3.16 informative morphogenetic variants/case), statistically very significant ($p<0.001$). The lowest value was obtained in subjects with mild retardation (1.45 informative morphogenetic variants/case) (p values represent the significance in comparison with the group with mild retardation).

Table 2. Mean value of morphogenetic informative variants per case in the subgroups of mentally retarded subjects.

Subgroup	Chromosomal disorder	Single gene disorders	Peri and postnatal lesions	Unknown etiology
Mean number	8.33	3	1.68	2.39
P value	p<0.001	p<0.001	p<0.01	p<0.001
Statistical significance	very significant	very significant	significant	very significant

„p" values represent the significance in comparison with the control group

DISCUSSION

Due to the progress in medical genetics, congenital origin of disability may be explored in an increasing number of affected subjects. Still, the etiology can still not be determined in all cases, although this would be necessary for the adequate treatment and for the genetic counseling.

Different studies have established that mentally retarded cases often have more informative morphogenetic variants than healthy subjects [9]. Similar findings were reported in subjects with

schizophrenia, learning disabilities, speech disorders, autistism and hyperactivity indicating that the presence of these informative morphogenetic variants is neither specific nor sensitive to a specific neurological or psychic disability. Due to this lack of specificity and sensitivity, the phenotypic classification has largely been ignored. We estimate that a comprehensive clinical morphology examination that classifies these cases as either phenotypically normal or abnormal would be a first step needed for establishing causally distinct subgroups.

Clinical morphology is a very powerful tool that helps identifying individuals whose development was disrupted during early embryogenesis. The role of clinical morphology in the successful delineation of the hundreds of syndromes that cause mental retardation suggested that it was a tool that might also help elucidate the heterogeneity within other neuropsychic disturbances. A comprehensive physical examination carried out by medical geneticists allows selection of subgroups of cases according to the the presence or absence of informative morphogenetic variants. The presence of these minor anomalies is a sensitive physical indicator of embryonic development, even if they are of no serious medical consequence. Some informative morphogenetic variants are reported to be present in healthy individuals [5]. They are of value to the clinical morphologist because they serve as indicators of altered morphogenesis that occurred early in embriogenesis and provide valuable clues in the diagnostic process. Their use is based on studies that have shown that informative morphogenetic variants are deviations from normal and that their presence predicts the presence of mental retardation or major anomalies of medical significance [6, 7].

A significantly increased number of informative morphogenetic variants in a subject with mental retardation provides strong evidence of an early prenatal contribution to the disorder. The defective gene or genes may have pleiotropic effects, as mental impairment is associated with different congenital anomalies. Informative morphogenetic variants are often the first indication of an underlying chromosomal disorder, a single-gene disorder or teratogenic exposure during embryogenesis. Studies that reported the association between minor anomalies and major anomalies or mental retardation have shown that the higher the number of minor anomalies, the greater the risk of medically significant defects [10]. Subjects with apparently normal physical development are less likely to have either a genetic or teratogenic disorder.

Our results, concordant with other studies from this field, reveal that the existence of more informative morphogenetic variants, especially more than 3 in the same subject, suggests the prenatal onset of mental retardation.

Since health state of infancy and childhood have a significant influence on the quality of life in adulthood, early diagnosis would be important in cases with neuropsychic disturbances and will certainly have long-term advantages[3]. The diagnosis and management of newborns can be complex and requires coordination of multiple disciplines.

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