Cognitive and psychosocial development in children with familial hypomagnesaemia

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Abstract. Aim. Familial hypomagnesaemia (FH) is a rare genetic condition. Neuromuscular and cardiovascular manifestations are well described, whereas cognitive and psychosocial development of children with FH is generally overlooked. Methods. Nine patients with FH were evaluated with psychiatric examination and psychometric tests for cognitive and psychosocial outcome. Results. Nine children (median age 10.1 yrs, range 3-16.3 yrs, 5 boys and 4 girls) with FH participated. Psychiatric symptoms were hyperactivity, irritability, sleep and speech problems and finger sucking. Common psychiatric diagnoses were Attention Deficit Hyperactivity Disorder, borderline intelligence, mild mental retardation and speech disorders. Parent-rated Child Behavior Checklist and Child Health Questionnaire mean scores were between 0.32-0.79, and 0.4-2.12, respectively; indicating the worsened psychosocial well-being besides considerable psychiatric diagnoses. Conclusions. Cognitive and psychosocial outcome in FH may influence morbidity, quality of life and social performance. Neuropsychiatric evaluation should be a routine part of management of children with FH.

Key words: familial hypomagnesaemia, cognitive, psychosocial, outcome

Familial hypomagnesaemia (FH) present in the neonatal period and infancy is a genetically determined, rare condition. With advances in molecular genetics, a number of disorders with familial hypomagnesaemia have been found, such as familial hypomagnesaemia with secondary hypocalcemia (HSH), isolated dominant hypomagnesaemia with hypocalciuria, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) and isolated recessive hypomagnesaemia with normocalciuria [1, 2].

The symptoms of hypomagnesaemia are abdominal pain, nausea, vomiting, lethargy, and weakness. In more pronounced magnesium depletion, symptoms of increased neuromuscular excitability predominate, such as tremor, carpopedal spasms, muscle cramps, tetany, and finally generalized seizures. Cardiac manifestations include atrial or ventricular tachycardia, premature contractions, a prolonged QT interval, and torsades de pointes [1]. Symptoms of hypomagnesemia do not necessarily correlate with serum magnesium levels.

Mental status changes are also seen and may include irritability, disorientation, depression, and psychosis in familial hypomagnesemia. However, only a few reports are available regarding cognitive and psychosocial outcome in primary hypomagnesaemia as a life-long disorder which may influence the morbidity, quality of life and social performance of those children [3, 4]. In this paper, we studied nine children with primary hypomagnesaemia in terms of cognitive and psychosocial outcome.
Patients and methods

The study group was nine patients with primary hypomagnesaemia from seven families who were followed up at the paediatric endocrinology clinic of Marmara University. Diagnosis of primary hypomagnesaemia was established by clinical, biochemical and molecular genetic (in 8 cases) evaluation (Guran et al., submitted for publication).

All patients were on maintenance magnesium treatment. The type of treatment and doses were adjusted according primarily to gastrointestinal tolerance and rate of seizures and secondarily to serum magnesium levels. All patients except F2.1 were treated with both oral and parenteral magnesium. As symptoms could not be controlled with oral treatment alone, weekly intramuscular MgSO₄ injections were added. F2.1 could not tolerate oral magnesium at all due to diarrhea so he was only treated with maintenance intramuscular MgSO₄ injections at weekly intervals. All the patients and families preferred parenteral magnesium substitutions and were compliant with the treatment. No adverse effects were observed during parenteral magnesium therapy. All patients experienced recurrence of symptoms during accompanying illnesses, such as common infections of childhood.

A clinical child psychiatric examination was followed by psychometric tests for neurodevelopmental and behavioral measures. The developmental levels of the children under 6 years of age were assessed using the Ankara Developmental Screening Inventory (ADSI). ADSI is a widely used developmental screening test for children under 6 years of age in Turkey and was developed by Savasir and colleagues [5]. The total raw scores of general development are converted to standard T scores, which are compared with the scores of children in the same age normative groups. Wechsler Intelligence Scale for Children Revised (WISC-R) is an intelligence test that yields the level of intellectual functioning in terms of Intelligence Quotient (IQ) [6]. It was administered to children between 6-16 years of age, using the Turkish adaptation made by Savasir and Şahin [7]. IQ levels are interpreted as normal or average intelligence (90-109); dull (80-89), borderline intelligence (70-79), and mild mental retardation (50-69).

The assessment of psychological adjustment incorporates a range of outcome measures including behavioral, emotional or psychosocial constructs. Therefore, The Child Behavior Checklist 2-3 (CBCL/2-3) [8] was utilized to obtain ratings of behavioral/emotional problems from parents of children below 3 years of age; it consists of 99 main items rated on a three-step response scale [9]. For the children above 3 years of age, parents filled out the CBCL 4-18 yrs version. For patients above 12 yrs of age, CBCL self reports were also completed by the children [10].

Quality of life is a multidimensional construct integrating an individual’s subjective perceptions of physical, social, emotional and cognitive functioning [11]. In the context of patient populations this is referred to as health-related quality of life. The Child Health Questionnaire (CHQ) was also administered as a generic health instrument designed to capture the physical and psychosocial well-being of children independently from the underlying disease [12]. The Turkish version of the CHQ is a reliable and valid tool for the functional, physical and psychosocial assessment of children [13].

Studies were performed with approval of the Ethics Committee of the Marmara University Faculty of Medicine, Istanbul, Turkey. Families of each participant provided written informed consent, and all studies were conducted in accordance with the principles of the Declaration of Helsinki.

Results

Nine children (median age 10.1 yrs, range 3-16.3 yrs, 5 boys and 4 girls) with primary hypomagnesaemia participated in the study. All the subjects except one (F4.1) were the product of consanguineous marriages. There were 2 pairs of siblings in study group originating from two different families with consanguineous parents. Genetic studies revealed familial hypomagnesaemia with secondary hypocalcemia (HSH) in 7 patients and familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) in one patient.

The neurodevelopmental and psychiatric findings of the nine patients are presented in table 1. Psychiatric symptoms presented in a wide range from hyperactivity, irritability to sleep problems, speech problems and finger sucking. Common psychiatric diagnoses were Attention Deficit Hyperactivity Disorder (ADHD), borderline intelligence, mild mental retardation and...
Table 1. The neurodevelopmental and psychiatric findings of patients with primary hypomagnesaemia.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Actual age (yrs)</th>
<th>Psychiatric symptoms</th>
<th>Psychiatric diagnoses</th>
<th>CBCL* (Parent-rated)</th>
<th>CBCL* (Self-reported)</th>
<th>CHQ**</th>
<th>ADSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1.1</td>
<td>M</td>
<td>16.25</td>
<td>Hyperactivity</td>
<td>ADHD</td>
<td>0.362</td>
<td>1.00</td>
<td>0.555</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nail biting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1.2</td>
<td>F</td>
<td>11.25</td>
<td>Irritability</td>
<td>ADHD</td>
<td>0.610</td>
<td>-</td>
<td>2.12</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aggressiveness</td>
<td>Borderline intelligence</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nail biting</td>
<td></td>
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<tr>
<td>F2.1</td>
<td>M</td>
<td>12.9</td>
<td>Stuttering</td>
<td>Mild mental retardation</td>
<td>0.442</td>
<td>0.232</td>
<td>0.931</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Animal phobia</td>
<td>Articulation disorder</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Sleep walking</td>
<td></td>
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</tr>
<tr>
<td>F3.1</td>
<td>M</td>
<td>10.1</td>
<td>Restricted social</td>
<td>Borderline intelligence</td>
<td>0.796</td>
<td>-</td>
<td>2.04</td>
<td>-</td>
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<td></td>
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<td>relations</td>
<td></td>
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<tr>
<td>F4.1</td>
<td>M</td>
<td>4</td>
<td>Speech problems</td>
<td>Expressive Language Disorder, NOS</td>
<td>0.380</td>
<td>-</td>
<td>0.4</td>
<td>Normal range</td>
</tr>
<tr>
<td>F5.1</td>
<td>M</td>
<td>9</td>
<td>Impulsivity</td>
<td>Mild mental retardation</td>
<td>0.592</td>
<td>-</td>
<td>1.38</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity</td>
<td>ADHD</td>
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<td></td>
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<td>Irritability</td>
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<td></td>
<td></td>
<td></td>
<td>Stereotypic</td>
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<td></td>
<td></td>
<td></td>
<td>movements</td>
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<tr>
<td>F5.2</td>
<td>F</td>
<td>3</td>
<td>Finger sucking</td>
<td>-</td>
<td>0.44</td>
<td>-</td>
<td>0.755</td>
<td>Normal range</td>
</tr>
<tr>
<td>F6.1</td>
<td>F</td>
<td>3.2</td>
<td>-</td>
<td>-</td>
<td>0.32</td>
<td>-</td>
<td>0.954</td>
<td>Normal range</td>
</tr>
<tr>
<td>F7.1</td>
<td>F</td>
<td>11.25</td>
<td>-</td>
<td>-</td>
<td>0.442</td>
<td>0.669</td>
<td>1.4</td>
<td>-</td>
</tr>
</tbody>
</table>

* The numbers indicate the total problem score of CBCL dividend by checklist questions. Higher scores indicate worsened behavioral well-being.
** The numbers indicate the total score of CHQ dividend by questionnaire questions. Higher scores indicate better physical and psychosocial well-being.

CBCL: child behavior checklist; CHQ: child health questionnaire; ADSI: Ankara developmental screening inventory; ADHD: attention deficit hyperactivity disorder, expressive language disorder.

In patients above 12 yrs of age completed CBCL self version and ADSI were administered to three children under six years of age which yielded normal neurodevelopmental levels (table 1).

In general, neuromuscular and cardiovascular manifestations of the hypomagnesaemia are well described and more frequently come to clinical attention. Although overlooked, the psychological development of these children with long-term hypomagnesemia is as important as other issues in terms of morbidity, life-quality and treatment costs. The literature is scarce in respect to psychiatric evaluation of hypomagnesemic children.

Discussion

In this study neurodevelopmental and psychosocial profiles of nine children from seven families with primary hypomagnesaemia were evaluated. There has been no previous evaluation of hypomagnesemic children with CBCL and CHQ. Thus, in the presence of extensive psychiatric evaluation as well as using related behavioral and life quality measures, we found that children diagnosed with hypomagnesaemia have considerable psychiatric diagnoses including; ADHD, mental retardation and speech disorder, in addition to worsened psychosocial well-being.

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Table 2. Comparison of the neurodevelopmental and psychiatric disorders of our patients with the incidence in the general population (according to [14]).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence in our cohort</th>
<th>Incidence in population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental retardation</strong></td>
<td></td>
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<tr>
<td>(limitations in mental functioning and in skills such as communicating, taking care of him or herself, and social skills that will cause a child to learn and develop more slowly than a typical child)</td>
<td>4/9</td>
<td>3/100</td>
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<tr>
<td><strong>ADHD</strong></td>
<td></td>
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<tr>
<td>(developmentally inappropriate levels of inattention and hyperactive-impulsive behavior)</td>
<td>3/9</td>
<td>3-5/100</td>
</tr>
<tr>
<td><strong>Articulation disorder</strong></td>
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<tr>
<td>(the inability to correctly produce speech sounds (phonemes) because of imprecise placement, timing, pressure, speed, or flow of movement of the lips, tongue, or throat)</td>
<td>2/9</td>
<td>2/100</td>
</tr>
<tr>
<td><strong>Parasomnia</strong></td>
<td></td>
<td></td>
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<tr>
<td>(sleep disorder that involves abnormal movements, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during sleep arousal)</td>
<td>1/9</td>
<td>25-30/100</td>
</tr>
</tbody>
</table>

Several psychiatric signs and symptoms have been described in patients with hypomagnesemia in rare adult case reports, including depression, agitation, disorientation, confusion, irritability, restlessness, auditory or visual hallucinations and psychosis [15]. In our study group, two patients qualified for the diagnosis of speech disorders. Aphasia was previously reported in a 3-year-old child with severe acute hypomagnesaemia [3, 15]. In older children with inadequate magnesium control, clouded sensorium and disturbed speech are often seen [4]. The exact mechanism of language dysfunction in patients with FH is not known. Increased numbers of N-methyl-D-aspartate-type glutamate receptors may be present in greater numbers in the temporal lobes as has been reported in a normal male who presented with acute and persistent loss of expressive language function and seizures caused by hypomagnesemia [16].

In our cohort, 2 out of 9 patients were diagnosed as having borderline intelligence and mild mental retardation. In Shalev et al.’s study; 2 of the 10 patients with FH had psychomotor retardation. Recurrent convulsions are blamed as a plausible explanation for mental retardation since others with fewer hypomagnesaemic-hypocalcaemic seizure attacks had normal psychomotor development [17]. Our patients with mental retardation had a similar number of convulsions per year compared to those with normal intelligence. Actually after the initiation of treatment they presented with tetany rather than convulsions. The age of presentation and number of convulsions before the diagnosis were also similar in our patients. Of interest, mentally retarded children in our cohort were relatively older than those with normal intelligence. Intelligence quotient scores and school performance were reported to be undisturbed by hypomagnesaemia in another study of only two cases [18]. In other diseases with magnesium wasting, like Gitelman’s syndrome, some psychological abnormalities, depressive state, paresthesia, paralysis and mental retardation have been reported [19, 20]. In previously reported sporadic cases, a good neurodevelopmental outcome could be achieved in those children who were treated with the adequate long term usage of enteral magnesium. Failure of early diagnosis of primary hypomagnesaemia or non-compliance with treatment recommendations can be detrimental, causing permanent neurological damage. Three of our patients (one third of the cohort) had ADHD, two of them from the same family (F1.1 and F1.2). Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder affecting some 5-10% children [21]. ADHD is defined by symptoms of inattentiveness and/or hyperactivity-impulsivity, impairment in at least two settings, and onset in childhood
In recent years, studies have indicated associations between hypomagnesaemia and ADHD [23-25]. Some studies have reported magnesium deficiency in children with ADHD syndrome [26-28]. It is reported that magnesium deficiency may reveal hyperactivity in susceptible children. The conclusion from the investigations is that magnesium deficiency in children with ADHD occurs more frequently than in healthy children and magnesium supplementation together with the standard traditional mode of treatment is recommended in ADHD children [28].

CBCL parent and self reports are widely used to assess psychopathology in both psychiatric cohorts and chronic disease groups worldwide [29, 30]. On the other side, CHQ is one of the most preferred health-related quality of life scales mostly used to measure both physical and psychosocial well-being of the child in the presence of a chronic illness [31, 32]. Our CBCL results were between normal and slightly higher range when compared to Turkish normatives [9, 10]. However the CHQ mean scores of our cohort lower than 1 point indicated worse psychosocial well-being when compared to healthy children, which were similar to the juvenile arthritis group results in Ozdogan’s study [13]. When the current literature about psychological examination of hypomagnesaemia is examined, no previous evaluations of children with CBCL and CHQ were found. Therefore, in the presence of extensive psychiatric evaluation as well as using related behavioral and life quality measures, we found that children diagnosed with hypomagnesaemia have considerable psychiatric diagnoses as well as worsened psychosocial well-being.

Non-compliance with treatment or inadequate management of magnesium treatment in the course of the disease, the effect of hypomagnesaemia itself on the central nervous system, and recurrent seizures due to delay in diagnosis of hypomagnesaemia might be among the reasons for disturbances in the neuropsychiatric outcome of children with primary hypomagnesaemia. Hypocalcemia may also contribute to the negative neuropsychiatric spectrum. Our study group represents a small number of children presenting with heterogeneous ages and treatment length. Therefore it is difficult to conclude that the neuropsychiatric outcome may depend on the time of diagnosis or degree of compliance with treatment. However, it seems that cases with familial hypomagnesaemia may face considerable neurodevelopmental co-morbidities because of the above-mentioned reasons.

Overall, mental retardation, ADHD and speech disturbances are more commonly seen in children with primary hypomagnesaemia which might prevent them from resuming a normal social life and might negatively affect treatment and education costs. Thus, we recommend that neuropsychiatric evaluation should be a routine part of the management of children with primary hypomagnesaemia.

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Disclosure

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