

MEDGEN

Developing Medical Genetics Education Through Curriculum Reforms
And Establishment Of Postgraduate Training Programs

Policy Brief of Medical Genetic Services in Armenia



TEMPUS

Genetic diseases contribute to a significant proportion of health problems. About 5.5% of the population are expected to develop a genetic or partly genetic condition by the age of 25. Fifty percent of admissions to paediatric hospitals are due to genetic and developmental disorders. One out of ten patients who consult primary care physicians and clinical specialists have diseases that are in part due to genetic factors.

Advances in knowledge of human genetics have led to a better understanding of the molecular basis of disease and has consequently resulted in improved clinical diagnosis and in novel approaches to prevention and treatment of genetic diseases. In parallel, the accompanying wide public awareness of these developments has raised expectations regarding more accurate assessment of genetic risk of individuals and within families and treatment of genetic disease.

During 2004-2008 the Council of Europe developed recommendations to member states on the impact of genetics on the organisation of health care services and training of health professionals; these have been accepted by the Committee of Ministers of Member States. The recommendation is in accordance with certified international guidelines (EuroGentest, EMQN, Orphanet) and are the base for the development of genetic services, education, and research in Armenia which is extremely important for the modern health care system of Armenia.

This genetic health policy brief is an objective analysis of current health care issues of this field in Armenia directed at a specific or a wider audience involved in or impacted by respective issues and who has the power and resources to implement the policy recommendations. The document involves several specific questions addressed to different groups of genetic/hereditary disorders and general questions regarding the access and quality of medical genetic services in Armenia:

Reference

European Health Committee (CDSP). Recommendation CM/Rec(2010)11 of the Committee of Ministers to member states on the impact of genetics on the organisation of health care services and training of health professionals.

Congenital Anomalies

What are congenital abnormalities?

As estimated 1 in 33 newborns is born with a congenital abnormality: these may be isolated or multiple and range from mild to severe. Between 2%-3% of birth complications and genetic malformations could develop due to maternal conditions during pregnancy, diabetes, viral infections in utero, etc. Multifactorial birth defects are caused by a combination of genes and environmental exposures. An environmental cause can increase the chance for the baby to be born with a birth defect, as 2%-3% of birth defects are caused by the exposure to teratogens or environmental agents (drugs, infections, alcohol, etc.). Some individuals inherit a gene variant that increases sensitivity to environmental triggers that may cause cleft lip or cleft palate, heart, neural tube and other defects. Chromosome abnormalities cause malformation syndromes with different set of birth defects. 20% of birth defects are associated with single gene mutations. About 70% of structural malformations are presumed to be multifactorial, meaning the siblings of the affected child could also have a higher risk of being affected, in comparison with healthy population. While 25% of structural malformations are caused by single-gene mutations or chromosomal abnormalities, in many cases a congenital anomaly may have no known cause.

What are the clinical features of congenital abnormalities?

About 150 types of structural malformations have been officially catalogued. The most common structural malformations are: cleft lip, which may be accompanied by cleft palate, talipes, in which feet (one or both) are twisted out of position, neural tube defects including spina bifida, dislocation of the hip in male and pyloric stenosis (mostly in males), when results in narrowing of the small intestine. About 60% of major birth defects are isolated and affect a single organ system such as heart, lip, etc. Some birth defects occur due to a common pathophysiological mechanism. An example is the restriction of mandibular growth before the 9th week of gestation that can cause the tongue to lie posteriorly, interfering with normal closure of the palatal shelves. Deformations are more common during the 2nd trimester of development when the fetus is constrained within the amniotic sac and uterus. Disruptions of developing tissue such as of amniotic sac causes different birth defects, including asymmetrical and irregular anomalies, the absence of normal tissue, variable limb anomalies, pseudosyndactyly, ankle constriction or amputation with disrupted toe development.

What are the psychosocial impacts of congenital anomalies?

Congenital anomalies may have significant impacts on individuals, families, health-

care systems and societies. Considering that children, by reason of their physical and mental immaturity, need special safeguards and care, promoting the health and well-being of children, with attention to the safety and quality of services, is important for the children as well as their families. In this regard, communicating with both parents and children (according to their age and maturity) enables them to be appropriately informed and involved in society. Clinical geneticists can prepare the parents emotionally and help them prepare for a child with a birth defect, especially if the condition is diagnosed before birth. All children require protection from physical, social, or emotional harm.

Who provides care for congenital abnormalities?

Primary health care physicians, pediatricians and neonatologists care for these newborns and children.

What are treatments and therapies for congenital anomalies?

Most birth defects cannot be cured; treatment focuses on managing the symptoms. In some cases there are ways to treat specific birth defects. Many congenital anomalies can be prevented, for example through , vaccination, adequate intake of folic acid and iodine, and adequate antenatal care. Paediatric surgeons treat a variety of congenital anomalies of the chest and abdomen. Some birth defects (such as urinary tract blockages and rare lung tumors) can be diagnosed and treated before birth (prenatally).

What problems and difficulties are associated with congenital abnormalities?

Costs associated are:

- Consultation with medical specialists such as a dysmorphologist, neonatologist, pediatrician, geneticist and/or child neurologist
- Diagnostic investigations using cytogenetic and molecular genetic testing, ultrasound examination, MRI
- Genetic counselling, including assessment of genetic risk, discussion of options (including future reproductive options) and support during decision making.

Some birth defects can be diagnosed before birth through ultrasound examination, amniocentesis or chorionic villus sampling (CVS). Most women should be offered non-invasive blood tests to determine the risk of having a baby with a specific birth defect (Down syndrome and spina bifida). Usually there is no possibility to cure a birth defect, so prenatal diagnosis may be the only way that parents can avoid having an affected child. In many cases a birth defect is diagnosed after birth through physical examination. When a congenital anomaly is discovered, a complete physical examination is important to avoid multiple malformations. A detailed examination should include: head, neck and facial features, skin, chest wall, heart,

lungs, abdomen, genitalia, anus, spine, back, extremities (including hands and feet), and neurological functions.

What is the role of genetic services in congenital anomalies?

- Prenatal diagnostics. Many birth defects (abnormalities and reduced fetal growth) are revealed during gestation and detected on ultrasound examination. Prenatal diagnostics could be available for many monogenic and all cytogenetically detectable chromosomal abnormalities. Neural tube defects can be also detected by prenatal diagnosis.
- Genetic counselling of family. A large proportion of spontaneous abortions and stillbirths are caused by chromosomal aneuploidy. Genetic counselling may be helpful for such cases and gives the opportunity for estimation of recurrence risk for family and early prenatal diagnosis in future pregnancies if the risk is significant (most aneuploidies occur sporadically). Genetic counseling for families having a child with congenital abnormality varies depending on the whether or not the genetic basis is revealed. The rate of recurrence for the members of the family could be estimated if the malformation is associated with known gene mutation or with environmental factor. Geneticists and dysmorphologists can diagnose teratogen-induced birth defects and explain their causes and risk for the family during genetic counseling.

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Autoinflammatory Disorders

What are hereditary periodic fever syndromes?

Hereditary periodic fever syndromes (HPFRs) are a group of monogenic disorders, characterized by recurrent attacks of apparently unprovoked inflammation that are caused by mutations in genes responsible for the regulation of innate immunity. Patients

suffering from HPRFs present with recurrent attacks of fever, abdominal, articular, and cutaneous signs of systemic inflammation in the absence of any infection, and often present with similar symptoms making their clinical diagnosis difficult. Today a definite diagnosis is made easier thanks to genetic analyses of mutations in causative genes for most HPRFs. International guidelines have been developed for molecular genetic testing of HPRFs based on the feedback received from International consortium experts in this field and these are intended to be used by health care professionals involved in the care of the patients. The most common and well characterized HRFr is the familial mediterranean fever (FMF), which mostly affects individuals of Armenian, Jewish, Turkish, and Arab ancestry.

What are the clinical features of FMF?

FMF is typically presenting in childhood or adolescence with 1-3 day episodes of fever, often accompanied by abdominal and/or chest pain, arthritis, and skin rashes. Between attacks, patients feel well in general and regain their normal daily functions until the next episode occurs, although biochemical evidence for inflammation may persist. One of the severe complications of the disease is amyloidosis, which mainly affects the kidneys. In cases with clinically suspected FMF genetic testing is recommended. If test is positive, the diagnosis of FMF is definite. Severity of FMF depends on the spectrum of mutations.

Who provides care for FMF?

In Armenia management of patients with FMF is generally engaged in two specialized centers - Center of Medical Genetics and Primary Health Care (adults) and the "ARABKIR" Joint Medical Center& Institute of child and adolescent health (children). Care for FMF is performed by family doctors, therapists, rheumatologists, nephrologists, pediatricians. The genetic testing of FMF is available at the Center of Medical Genetics and Primary Health Care (CMG).

What are treatment and recommendations for people with FMF?

There is no cure for FMF as it is a genetic disease. The patients with confirmed diagnosis are treated with life-long use of colchicine as the gold standard for treatment of FMF. Daily oral intake of colchicine efficiently reduces the frequency and severity of FMF attacks, and usually prevents the development of amyloidosis. The prognosis of FMF is good with early diagnosis and daily colchicine treatment. Patients being treated should have blood and urine tests for at least twice a year. There is no specific diet for FMF patients. Patients are generally not restricted regarding in playing sport, the exception being patients with protracted joint inflammation as the activity may cause limitation of motion of affected joints. Colchicine is recommended during pregnancy,

because it prevents febrile attacks of FMF, reduces risk of miscarriages and renal complications. There are no significant data about negative consequences of colchicine on male fertility.

What are the psychosocial impacts of FMF?

The child and the family often experience major problems before the disease is diagnosed as the parents have to take the child to a hospital frequently because of severe abdominal, chest, or joint pain. Some children undergo unnecessary surgery due to misdiagnosis. After the diagnosis is confirmed, the main problem could be the psychological burden of life-long treatment. Some children initially need psychological support to cope with the disease, which means lifelong uptake of medications, and patient-parent education program can help to overcome this problem. Most children, however, adapt to the treatment, and when well controlled, FMF should not interfere with a normal education and productive adult life. Attacks of FMF may be precipitated by factors such as emotional or physical stress or exposure to cold. Patients recognize the state that precedes the attacks, and may in some cases become irritable, have dizziness, and lack of appetite. The repeated crises and intense pain result in a negative psychological impact on the patient including depression.

What is the role of genetic services in FMF?

In Armenia, both genetic counselling and genetic testing of FMF are performed in one specialized center –the Center of Medical Genetics and Primary Health Care. As FMF is an autosomal-recessive genetic disease, each child of carrier parents has a 25% chance of inheriting two mutations, one from each parent. However, in about 8% of Armenian patients only one mutation causes clinical symptoms of the disease. The risk of inheritance of FMF in families is estimated during the genetic counselling by clinical geneticists. Prenatal diagnosis of FMF is not recommended, according to international guidelines for genetic diagnosis of HPFRs. Therefore, genetic analysis of FMF mutations is recommended for:

- confirmation of the diagnosis of FMF in suspected and atypical cases of the disease
- prognosis of development of the complications of the disease
- determination of carrier status in family members of FMF patients
- informing genetic counselling of FMF patients and families.

What problems and difficulties are associated with FMF?

Costs associated with FMF:

- Specialist (MDs) consultation

- Clinical and genetic diagnostics
- Treatment and follow-up
- Genetic counselling.

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Inborn Errors of Metabolism

What are Inborn Errors of Metabolism?

Inborn Errors of Metabolism (IEM) comprise a group of disorders in which a gene defect causes a clinically significant block in a metabolic pathway, resulting either in accumulation of substrate behind the block or deficiency of the product. More than 500 metabolic diseases are known; almost all are classified as orphan diseases and each has its own requirements for diagnosis and treatment. The inheritance of most IEMs is rare and all are genetically transmitted typically in an autosomal recessive or X-linked recessive way. IEM disorders may manifest at any stage of life, from infancy to adulthood. Early identification of IEM correlates with significant reduction in morbidity, mortality, and associated disabilities for those affected. The major categories of IEMs are:

- Organic acidemias
- Fatty acid oxidation defects
- Primary lactic acidoses
- Aminoacidopathies (phenylketonuria, hereditary tyrosinemia, nonketotic hyperglycinemia, maple syrup urine disease and homocystinuria)

- Urea cycle defects (citrullinemia, ornithine transcarbamylase deficiency, and arginosuccinic aciduria)
- Disorders of carbohydrate metabolism (galactosemia, hereditary fructose intolerance, fructose 1,6-diphosphatase deficiency and the glycogen storage diseases)
- Lysosomal storage disorders (mucopolysaccharidosis, Tay-Sachs, Niemann-Pick disease, Gaucher's disease)

What are the clinical features of IEM?

The number of known metabolic disorders is probably as large as the number of presenting symptoms that may indicate metabolic disturbances. Clinical findings suggestive of IEMs may include:

- History of consanguinity, mental retardation, or sudden infant death syndrome; symptom onset with institution of feedings or formula change; history of growth disturbances, lethargy, recurrent emesis, poor feeding, rashes, seizures, hiccoughs, apnea, tachypnea.
- Physical findings: tachypnea, apnea, lethargy, hypertonicity, hypotonicity, hepatosplenomegaly, ambiguous genitalia, jaundice, dysmorphic or coarse facial features, rashes or patchy hypopigmentation, ocular findings (cataracts, lens dislocation or pigmentary retinopathy), intracranial hemorrhage, unusual odors.
- Laboratory findings: metabolic acidosis with increased anion gap, primary respiratory alkalosis, hyperammonemia, hypoglycemia, ketosis or ketonuria, low blood urea nitrogen, hyperbilirubinemia, lactic acidosis, high lactate/pyruvate ratio, non-glucose-reducing substances in urine, elevated liver function tests, neutropenia and thrombocytopenia.

What are the psychosocial impacts of IEM?

Many individuals with IEMs experience psychological symptoms secondary to the pathophysiology of the disease or as a result of psychosocial stressors inherent in living with chronic illness. Similarly, parents and families experience psychological distress as the result of having a loved one with an inborn error. Increased stress, mood disorders, interpersonal challenges, decreased quality of life, and grief reactions are all common for patients and their families. Even early and well-treated patients experience hidden disabilities, including subtle deficits in executive functioning, mild reductions in mental processing speed, social difficulties, and emotional problems that may remain unnoticed for years. Psychosocial aspects may also include social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, and having healthy emotional development.

Who provides care for IEMs?

Management and care of these complex, lifelong, multisystem metabolic disorders often requires a coordinated, multidisciplinary approach involving several subspecialists and which may include complex laboratory evaluations, genetic counselling, nutritional therapy, and unusual therapeutic approaches that have been used in only a small number of cases. Frequently, inborn errors of metabolism fall outside current standard diagnostic and treatment guidelines of managed care plans. This results in delays in diagnosis and appropriate management, with increased costs to patients and to society. Many genetic IEMs cannot be prevented, but severe symptoms (such as mental retardation) as a consequence can be prevented if the disease is diagnosed and an appropriate treatment is met (for example, correct diet). In Armenia, the lack of specialists and care system for IEMs is obvious and only in some cases, such as PKU and hyperthyroidism, the diagnostics and care has slightly moved forward. Generally, routine screening for IEMs is not standard practice for newborns in Armenia (except for PKU and hyperthyroidism).

What are treatments and therapies for IEMs?

Although treatment differs for each specific disorder, each should be managed by considering the potential disease category and by following the subsequent steps, along with consultation with a metabolic specialist. The major approach is the following:

- Hydration/nutrition/acid-base management;
- Elimination of toxic metabolites: treatment of hyperammonaemia is urgent;
- Evolving therapies include organ transplantation and enzyme replacement.

Even when no effective therapy exists or when an infant dies from a metabolic disorder, the family still needs an accurate diagnosis for clarification, reassurance, genetic counselling, and potential prenatal screening. In Armenia, treatment is given based on the patient's symptoms and if IEM is confirmed, it is treated by alterations in diet.

What problems and difficulties are associated with IEMs?

Costs associated with IEMs are:

- Specialist (MD) consultation
- Diagnostics
- Management, care, counselling.

What is the role of genetic services for IEMs?

The role of genetic services for IEMs is:

- to provide genetic diagnostics for clinically diagnosed patients
- to determine the carrier status of individuals with the particular genetic burden

- to provide genetic counselling for patients and families
- to provide information of estimated risk to the families having history of IEMs.

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Neuromuscular Diseases

What are Neuromuscular Disorders?

A neuromuscular disease is a disorder that affects the peripheral nervous system, which includes muscles, the neuromuscular junction, peripheral nerves in the limbs, and the motor-nerve cells in the spinal cord. Neuromuscular disorders (NMD) include many different syndromes and diseases that either directly or indirectly impair the function of the skeletal muscles. This can be through problems with the muscle pathology or problems found in the signal that is sent to the muscle through a nerve. When problems arise in the muscle itself this often occurs in the muscle cell membrane. Alterations in the membrane structure are often a result of change in the genetic information found within cells. These genetic changes are called gene mutations. Gene mutations can be the result of a new mutation or inherited, having been passed through generations in a family. The field of inherited NMDs has become very complex, with over hundred genetically distinct forms of myopathies, neuropathies, and mitochondrial disorders identified in the last few decades.

What are the clinical features of NMDs?

All NMDs are progressive in nature and all result in muscle weakness and fatigue. Some diseases are present at birth, some manifest in childhood, and others have an adult onset. Patients with NMDs can have weakness, loss of muscle bulk, muscle twitching, cramping, numbness, tingling, and other symptoms. Problems with the neuromuscular junction can

also cause drooping eyelids, double vision, and weakness that worsens with activity. Some NMDs can also cause difficulty with swallowing and sometimes with breathing. The clinical manifestation of cardiac disease in NMDs is common and their management should include both periodic cardiac assessment and appropriate symptomatic and definitive therapy. Dilated cardiomyopathy is also a common complication.

What are the psychosocial impacts of NMDs?

Depending on the type of disorder, the worsening of functional control gradually alters the child's abilities, which manifests itself through decreased effort tolerance, increased fatigue, increasing loss of strength, physical and vibratory sensitivity, ambulation, balance and coordination. A developmental disability or a severe learning disorder may sometimes accompany neuromuscular diseases. The psychological impacts of NMDs are of great significance. Adjusting to a neuromuscular disease triggers many contradicting emotions such as resignation, passiveness or helplessness, and also rage, anger, frustration or intolerance. Some people manage to reach a point of pain withdrawal, regret or limitations given the severity of such a degenerative disease on a child's life. Denial and hope are also coping mechanisms. The impact of NMDs on a young child's social participation depends on child's deterioration profile, situations of handicap may not occur until the age of 2, 8 or even 15 years.

Who provides care for NMDs?

Receiving the best care can dramatically improve patients' quality of life and prolong life expectancy. In developed countries, the health and educational systems provide sufficient care for NMDs. Physicians, pathologists, geneticists, nurses, health care providers, psychologists and social therapists are involved in caring for patients with neuromuscular diseases. In Armenia such multidisciplinary approach in providing care for NMDs is lacking. After visiting family doctors patients occasionally being sent to the specialist or/and geneticist. In successful cases, care will include:

- creatine phosphokinase (CK) estimation in the blood serum
- EMG
- genetic testing (if it is available in Armenia)

From the numerous NMDs the followings are genetically tested in Armenia:

- Duchenne and Becker muscular dystrophy
- spinal muscular atrophy

Because of the complexity of medical problems associated with the diagnosis of NMDs, the importance of family education and genetic counseling is crucial. The

primary care physician (pediatrician or family physician) should be well informed of the multidisciplinary needs of these patients and must play a central role in coordinating follow-up care.

What are treatments and therapies for NMDs?

General treatments aim at optimizing muscle strength and function and are the following:

- steroid use has greatly improved the quality of care and life of patients. In Armenia standards are kept for steroid treatment: depending of the age and symptoms of the patients' prednisolone is prescribed.
- intravenous immunoglobulin (IVIG): in Armenia IVIG is available and may be used in case of indication.
- plasmapheresis: This dialysis-like treatment is reserved for patients with acute decompensations in serious NMDs. In Armenia plasmapheresis is available and international standards are maintained.
- immunosuppressive therapy: The use of a variety of immunosuppressive drugs such as methotrexate, mycophenolate, azathioprine, cyclophosphamide, rituximab is available in Armenia and may be used when indicated.
- In Armenia, patients undergo regular risk stratification for sudden cardiac death and symptoms such as heart failure and treated with suitable medical therapy.
- psychosocial management includes psychotherapy, pharmacological interventions, social interaction interventions, educational interventions, care-support interventions. In Armenia, psychosocial management is lacking and dynamic services must be established to enable patients to obtain appropriate assistance.

What problems and difficulties are associated with NMDs?

Costs associated NMDs are:

- specialist (MD) consultation
- diagnostic tests
- management, care and counselling.

What is the role of genetic services for NMDs?

The role of genetic services for NMDs is:

- to provide genetic diagnostics for clinically diagnosed patients
- to determine the carrier status of individuals with the particular genetic burden
- to provide genetic counselling for patients and families
- to provide information of estimated risk to the families with a history of NMD.

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Neurodevelopmental Disorders

What are the etiological factors of neurodevelopmental disorders?

Neurodevelopmental disorders, including intellectual disability (ID) and autism spectrum disorders (ASD) are a grouping of a large and heterogeneous collection of syndromic and nonsyndromic disorders that have impaired intellectual abilities as a common hallmark. Neurodevelopmental disorders can be caused by genetic defects as well as environmental insults that affect the development and functioning of the nervous system, prenatally, perinatally, or postnatally. The most common environmental factors are malnutrition during pregnancy, pre- and postnatal infections, fetal alcohol syndrome, exposure to other neurotoxic compounds, premature birth, and peri- and postnatal asphyxia or other traumas which have a major contributing role to the prevalence of mild ID. Genetic causes of neurodevelopmental disorders are more frequently observed in the group of severe ID and include chromosome abnormalities, genomic and monogenic diseases. Such causes account for up to 65% of moderate-to-severe ID. Autism is another condition for which prevalence appears to have increased over the last two decades. Although it is thought to have a genetic component, little is known about risk factors for autism. It occurs in at least 1% of children. Some of the reported increase, however, is likely to be attributable to increased awareness, new administrative classifications and diagnostic practices.

What are the clinical features of neurodevelopmental disorders?

Clinically, ID is defined by three criteria: i) significant sub-average general intellectual functioning; ii) limitations in adaptive behaviour in at least two of the following skills: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety; iii) onset of the symptoms before 18 years of age. The classification of intellectual disability is mostly based on the measurements of Intellectual Quotient (IQ) tests. From a clinical perspective, ID is subdivided into two major categories - syndromic, characterized by associated clinical, radiological, metabolic or biological features, and non-syndromic forms of ID in which the cognitive impairment represents the only manifestation of the disease. Also, three major groups of ID associated disorders have been defined:

metabolic syndromes, syndromes with ID and associated malformations/dysmorphisms and syndromes with ID and neurological/neuromuscular symptoms.

Symptoms of ASD vary, but in general, they fall into two areas: social impairment, including difficulties with social communication, and repetitive and stereotyped behaviors. Children with ASD do not follow typical patterns when developing social and communication skills. Parents are usually the first to notice unusual behaviors in their child.

What are the psychosocial impacts of neurodevelopmental disorders?

Many children and young people with neurodevelopmental conditions, however, experience a number of impairments and co-morbidities which, in conjunction with restrictions and barriers to participation, result in complex medical, educational and social support needs. Children with neurodevelopmental impairments/ conditions appear to be at higher risk than their non-disabled peers of all forms of violence, including abuse and neglect by parents/carers, peers and others. The biggest barrier faced by anyone with any form of neurodevelopmental disorders is having their potential recognized and realized. Two common social and psychological impacts on the person with a neurodevelopmental disorder are i) low expectations of the person with a neurodevelopmental disorder held by families, teachers, trainers, or support workers, which generally have negative consequences for his/her self-esteem, and ii) learned helplessness. The social and psychological impacts of neurodevelopmental disorders are more complicated in families where neurodevelopmental disorder of a child is known to have genetic bases. Parents have enormous emotional problems and suffer from mental worries not only because they have a child with a neurodevelopmental disorder, but also the chance of the recurrence of the disease in the family, which emphasizes the importance of timely genetic counselling and prenatal genetic testing.

What are treatments for people with neurodevelopmental disorders?

ID has been considered as neurodevelopmental disorder with irreversible cognitive deficits. However, neurological effects of some gene mutations can be ameliorated during adulthood. The best known example of successful adult rescue of a learning and memory deficit has been obtained for fragile X syndrome. The relatively rare involvement of individual genes in most ID conditions is a problem for the development of therapeutic strategies. However, drugs targeted toward common molecular and cellular pathways where many ID genes are converged, could have a beneficial effect for a much larger group ID disorders. Therefore, improvement of symptoms, including intellectual impairment, is possible for some forms of ID and modulation of underlying common pathways by drugs can become a realistic approach to improve the quality of life for patients and families confronted with these conditions. ASDs are often accompanied by significant lifelong impairments. Individuals with ASDs often require intensive parental, school, and other social support. In addition to intensive behavioral therapies, services

at school ranging from individualized education plans with combinations of speech therapy, social skills training, and physical therapy are required for most children with ASDs. While there's no proven cure yet for ASD, treating ASD early, using school-based programs, and getting proper medical care can greatly reduce ASD symptoms and increase child's ability to grow and learn new skills.

Who provides care for genetic/hereditary forms of neurodevelopmental disorders?

In Armenia the Center of Medical Genetics and Primary Health Care provides genetic testing for neurodevelopmental disorders caused by chromosome abnormalities, genomic or gene defects. The genetic testing for neurodevelopmental disorders is usually ordered by a physician or genetic consultant. As for any genetic testing, written informed consent is strongly required before a genetic test is ordered. People give their consent by signing a form saying that they have been told about, and understand, the purpose of the test, its medical implications, the risks and benefits of the test, possible alternatives to the test, and their privacy rights.

What problems and difficulties are associated with inherited/genetic forms of neurodevelopmental disorders?

Because of heterogeneous etiology and overlapping phenotypic spectra, specific genetic defects are rarely diagnosed in affected children and the real incidence of genetic alterations in neurodevelopmental disorders are still not well determined. Even applying the latest technologies of diagnostics, up to 60% of cases remain undiagnosed. Another important issue is the nature of the genetic aberration - de novo or inherited which requires the further analysis of parents to provide accurate recurrence risk of the disease. Meantime, in Armenia due to several socio-economic conditions the timely genetic counseling of neurodevelopmental disorders remains inaccessible for majority of families, particularly because of the higher costs of investigations for diagnosis, which increases the chances of birth of the second child with the same condition in case of hereditary neurodevelopmental disorder.

What is the role of genetic services in neurodevelopmental disorders?

Increased identification of some conditions has resulted in increasing demand for diagnostic and support services, and welfare benefits for children, young people and their families. In Armenia, both genetic counseling and genetic testing of genetic/hereditary bases of neurodevelopmental disorders are performed only in the Center of Medical Genetics and Primary Health Care. Genetic tests are usually requested by a person's physician, pediatrician, or other health care provider. Accurate information about a complex strategy of genetic diagnosis of neurodevelopmental disorders is provided

during the genetic counseling. The best approach to the genetic evaluation of a child with a neurodevelopmental disorder is to do a careful medical history, family history, and dysmorphic and neurologic examination. Based on this alone, a geneticist suspects or establishes a diagnosis in as many as two thirds of cases. Depending on the heterogeneous genetic etiology of syndromic and non-syndromic neurodevelopmental disorders (chromosomal rearrangements, X-linked and autosomal), testing, diagnosis, and calculation of the recurrence risk can widely vary. Genetic testing is done on a small sample of blood (both for cytogenetic and molecular genetic analyses), and then the laboratory returns the test results to the physician or genetic counselor. Only specialized genetic counsellor, clinical geneticist or doctor trained in genetics can perform genetic counselling in these cases. Being able to provide a genetic etiology allows for the opportunity of prenatal diagnosis, guidance with disease management, acceptance of the disability, and connection with other parents and support groups.

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Hereditary Cancer Syndromes

What are hereditary cancer syndromes?

Cancer is a common disease, and the etiology of cancer is multifactorial, with genetic, environmental, medical, and lifestyle factors interacting to produce a given malignancy.

Hereditary cancer is cancer risk that is inherited or passed on in a family. About 5-10% of all cancers are considered to be hereditary. Hereditary cancer is suspected if there are multiple people in the family with related types of cancer, including more than one generation of family members with the disease. In addition, people diagnosed at a young age are more likely to have hereditary cancer. Knowing the different cancers associated with a cancer syndrome allows family members to undergo earlier and more frequent cancer screening.

What are the features of hereditary cancer?

Clinical and anamnestic features that may suggest a hereditary cancer syndrome include:

- ✓ Cancer that was diagnosed at an unusually young age,
- ✓ Several different types of cancer that have occurred independently in the same person,
- ✓ Multiple primary tumors that have occurred independently in the same organ,
- ✓ Tumors with rare histology,
- ✓ Tumors associated with another rare disease or other genetic traits,
- ✓ Tumors associated with an inherited precursor lesion,
- ✓ Cancer that has developed in both organs in a set of paired organs,
- ✓ Unusual cases of a specific cancer type (for example, breast cancer in a man), and
- ✓ The presence of birth defects, such as certain benign skin growths or skeletal abnormalities, that are known to be associated with inherited cancer syndromes.

In the patient's family important features of hereditary cancer syndrome are:

- ✓ One first-degree relative with the same or a related tumor and one of the individual features listed above or several close blood relatives that have the same type of cancer, tumor of the same site, tumor types belonging to a known familial cancer syndrome, or rare tumors.

What are the psychosocial impacts of hereditary cancer syndromes?

Information about familial cancer risk may have psychological effects or social costs (worry, guilt, or increased health care costs). Family dynamics also may be affected. For instance, the involvement of one or more affected family members may be required for genetic testing to be informative, and parents may feel guilt about passing inherited risk on to their children.

Who provides care for hereditary cancer syndromes?

In Armenia the genetic testing is available only for hereditary breast cancer and ovarian

cancer syndrome at the Center of Medical Genetics and Primary Health Care. The genetic testing for cancer is typically ordered by a physician. Written informed consent is strongly required before a genetic test is ordered.

What are recommendations for people with a strong inherited cancer risk?

When the person has a personal or family history that suggests an inherited cancer risk condition, he/she should be strongly considered for genetic counselling. Cancer genetic counselling includes a detailed review of the individual's personal and family medical history related to possible cancer risk, and may involve several family members, some of whom will have had cancer and others who have not. The information derived from risk assessment and/or genetic testing allows the health care provider to intervene earlier either to reduce the risk or diagnose a cancer at an earlier stage, when the chances for effective treatment are greatest. The information may be used to modify the management approach to an initial cancer, clarify the risks of other cancers, or predict the response of an existing cancer to specific forms of treatment, all of which may alter treatment recommendations and long-term follow-up.

What problems and difficulties are associated with inherited cancer syndromes?

Identification of an individual at increased risk of developing cancer may have important, potentially life-saving management implications and may lead to specific interventions aimed at reducing risk (e.g., tamoxifen for breast cancer, colonoscopy for colon cancer, or risk-reducing salpingo-oophorectomy for ovarian cancer). In patients who have already been diagnosed with cancer, a positive result for a mutation associated with certain hereditary cancer syndromes can influence how the cancer is treated and the offer of counselling for biological relatives. If someone with one of these conditions receives a standard dose of radiation or chemotherapy, they may experience severe, potentially life-threatening treatment side effects. Knowing about the genetic disorder before treatment begins allows doctors to modify the treatment and reduce the severity of the side effects.

However, even if a cancer-predisposing mutation is present in a family, it does not necessarily mean that everyone who inherits the mutation will develop cancer. Several factors influence the outcome in a given person with the mutation. One factor is the pattern of inheritance of cancer syndromes. The severity of the symptoms may also vary from person to person. Information about familial cancer risk may also inform a person's ability to plan for lifestyle and health care decisions, family planning, or other decisions. Simultaneously, if a family is known to carry a cancer-predisposing mutation in a particular gene, family members may experience reduced worry and lower health care costs if their genetic tests indicate that they do not carry the family's disease-related mutation.

What is the role of genetic services in hereditary cancer syndromes?

In Armenia, both genetic counselling and genetic testing of inherited cancer syndromes are performed at the Center of Medical Genetics and Primary Health Care. Genetic tests are usually requested by a person's doctor, oncologist or other health care provider. Principally, before and after the genetic testing, genetic counseling is performed to make sure that patients have accurate information about a particular genetic test. Genetic testing is done on a small sample of body fluid, and then the laboratory returns the test results to the doctor or genetic counselor. Genetic testing can have several possible results: positive, negative, false negative, variant of unknown significance, or benign polymorphism, etc. A specialized genetic counsellor, clinical geneticist or doctor trained in genetics should be available to help an individual or family understand their test results. Such counselling includes discussing recommendations for preventive care and screening with the patient, and providing emotional support to the person receiving the results. In general, physicians rely on the family member who has been tested to share the genetic information with their relatives who could be at high cancer risk.

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Leukaemias

What are leukaemias?

Leukemia is a type of cancer that affects the blood and bone marrow. The disease develops when blood cells produced in the bone marrow grow out of control. Leukaemia, like other cancers, results from mutations in the genes, which may occur spontaneously or as a result of exposure to radiation or carcinogenic substances. The four most common types of leukaemia are acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML), and chronic lymphocytic leukaemia (CLL). Each main type of leukaemia

is named according to the type of cell that is affected (a myeloid cell or a lymphoid cell) and whether the disease begins in mature or immature cells.

What are the clinical features of leukemias?

Leukaemia can present with a variety of symptoms with a wide differential. Patients with leukaemia can have fatigue, dizziness and palpitations, severe and unusual bone and joint pain, recurrent and severe infections (oral, throat, skin, perianal infections commonly), fever without obvious infection (but infection should be assumed), left upper quadrant fullness and early satiety due to splenomegaly (10-20%), dyspnoea, headache, irritability or altered mental status and neck stiffness, haemorrhagic or thrombotic complications due to thrombocytopenia or disseminated intravascular coagulopathy, frequent nosebleeds or spontaneous bruising.

What are the psychosocial impacts of leukaemias?

Distressed psychological states are common in individuals with leukaemia. The prevalence of psychological distress varies by time since diagnosis, degree of physical and role impairment, amount of pain, prognosis and other variables. Chronic illness can bring about guilt, feelings of loss of control, anger, sadness, confusion and fear. Anxiety, mood disturbance, fear of recurrence, concerns about body image, and communication and other problems with family members are common in cancer patients as well. Patients may also experience more generalized worry, fear for the future, inability to make plans, uncertainty and a heightened sense of vulnerability, and other worries. Moreover, cancer patients can face spiritual and existential issues involving their faith and the possibility and meaning of death. Some survivors report feelings of anger, isolation and diminished self-esteem in response to such stress.

Who provides care for patients with leukaemia?

To confirm the diagnosis and identify the specific type of leukemia, a needle biopsy and aspiration of bone marrow from a pelvic bone will need to be done to test for leukaemic cells, DNA markers and chromosome changes in the bone marrow. Many recurring genetic abnormalities in the lymphoid and myeloid neoplasms can be identified by molecular genetic or cytogenetic analyses, but cytogenetic studies should be performed initially and at regular intervals throughout the course of the disease to establish a complete genetic profile and to detect genetic evolution. Important prognostic factors in leukaemia include the age of the patient, the type of leukaemia, and the chromosomal abnormalities found in leukaemia cells and bone marrow. Genetic testing is available for ALL, AML, and CML at the Center of Medical Genetics and Primary Health Care. The genetic testing for diagnosing leukaemia and for further monitoring is typically ordered by a hematologist. The right diagnostics can dramatically improve patients' quality of life and prolong life expectancy.

What are treatments and therapies of leukaemias?

The goal of treatment for leukaemia should be complete remission - that the cancer goes away completely for a minimum of five years after treatment. Treatment destroys the leukaemia cells and allows normal cells to form in bone marrow. Treatment decisions are based on the kind of leukaemia, its stage, the patient's age and general health.

Patients with ALL and AML need to start treatment soon after diagnosis. Usually, they begin treatment with chemotherapy. Postremission therapy is usually needed even after a patient is in remission, which may include chemotherapy with or without stem cell transplantation. Patients newly diagnosed with CML need immediate treatment with one of three approved drugs - imatinib mesylate, dasatinib, or nilotinib, which do not cure but keep CML under control for many patients for as long as they take it. Allogeneic stem cell transplantation is another treatment option that is only done if CML is not responding as expected to drug therapy. Some CLL patients do not need treatment for long periods of time after diagnosis. Patients who need treatment may receive chemotherapy or monoclonal antibody therapy alone or in combination. Allogeneic stem cell transplantation is a treatment option for certain patients, but usually not as the first choice of therapy

What costs are associated with genetic/hereditary disorders?

Costs associated leukemias are:

- haematologist (MD) consultation
- diagnostic tests
- treatment (chemotherapy, special antibiotics, injections, blood transfusions, and more)
- stem cell transplantation
- additional costs for transportation, hospitalization and supportive care.

What is the role of genetic services?

The role of genetic services for leukaemias is:

- to provide genetic diagnostics, which is necessary to confirm the diagnosis and identify the specific type of leukemia
- to determine the genetic alterations, which can give information on a person's prognosis (high risk, medium risk, low risk)
- to advise on certain types of treatment, dependant on specific genetic alterations (translocations, deletions etc.)
- to monitor the disease, based on the primary alterations
- to provide genetic counselling for patients and families.

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Genetic Problems of Reproduction

What are genetic factors of reproductive failure?

Reproductive failures include a wide variety of problems - infertility, pregnancy loss, abnormal pregnancy and birth defects. The cause of almost any reproductive abnormality can be the result of genetic and/or physiological events that occur in mother, father and/or fetus. Mutant genes and chromosomal disorders can disturb gamete formation and impair normal embryonic development. Approximately 15-20% of clinically recognizable pregnancies end in spontaneous abortion. The incidence of chromosome abnormalities in those abortions is 40-50%. The clinical consequences of development of abnormal gametes with unbalanced chromosome sets include sterility, repeated spontaneous abortions and birth of malformed children, which emphasizes the importance of the definition of the genetic cause of the abortion.

What are the features of reproductive failure?

Reproduction failure can be absolute (infertility, spontaneous abortions, and stillbirths) or relative (congenital malformation, genetic syndromes and mental retardation). The prevention and control of reproductive failures begin with the study of etiology and necessitate multidisciplinary investigations. Among those, genetic investigations are of great importance.

What are the psychosocial impacts of reproductive failure?

The wish for a child is one of the most basic of all human motivations. For women, pregnancy and motherhood are developmental milestones that are highly emphasized

by our culture. When attempts to have a child fail, it can be an emotionally devastating experience. The fact of reproductive failure may have psychological effects on the family and also social costs. Lack of knowledge of the cause which can lead to reproductive failure triggers the sense of anxiety, guilt and also increased health care costs.

Who provides care for reproductive failure?

Traditionally patients with different recurrent pregnancy loss are evaluated by numerous healthcare providers as they require specialist care by a team that may include a gynaecologist, obstetrician, endocrinologist, immunologist and geneticist. It is important to provide such multidisciplinary approach before pregnancy. In Armenia genetic testing (molecular and cytogenetic) is available at the Center of Medical Genetics and Primary Health Care. Along with recognition of the carriers with chromosomal rearrangement in couples, there is prenatal care strategy to prevent miscarriage and the birth of a child with chromosomal abnormalities. There is a non-invasive screening procedure to detect risks of aneuploidy through maternal blood tests for different specific substances during first and second trimester of pregnancy. These tests do not diagnose an abnormality; they only signal that further testing with invasive procedures should be offered.

What problems and difficulties are associated with genetic causes of reproductive failure?

There is a lack of genetic service delivery in Armenia to decrease reproductive failure manifested as early miscarriage. On the other hand, prenatal screening tests have not been delivered in full to pregnant women, since every pregnancy should be considered as a risk event. This is the matter of strong national policy to provide such multidisciplinary approach. The costs of recognition of genetic factors in cases of recurrent pregnancy loss include genetic consultation, diagnostics, and management of patients.

What is the role of genetic services in reproductive failure?

During genetic counselling clinical geneticist takes a detailed medical, surgical, family, and genetic history. Genetic examinations that may be done include:

- ✓ cytogenetic analysis of the parents to investigate potential chromosomal rearrangements in the parents that could be passed in an unbalanced form to the offspring, resulting in miscarriage. Chromosomal rearrangements in parents are a major pre-disposing factor and causative of abortion if passed in an unbalanced form to the embryo. Individuals in whom a cytogenetic abnormality is found are often referred for genetic counselling, where the clinical geneticist discusses about the genetic abnormality and the likelihood of having a chromosomally normal or abnormal pregnancy in future. The actual risk will depend on the parental chromosome rearrangement. Affected couples may choose to undergo prenatal

genetic examination during pregnancy to check the genetic make-up of the offspring. Cells for analysis can be obtained via either 1) chorionic villus sampling late in the first trimester or early in the second trimester, or 2) amniocentesis in the second trimester.

✓ maternal blood analysis to detect elevated level of homocystein at an early stage of pregnancy, which correlates with MTHFR gene mutations and is associated with fetal neural tube defects, various conditions characterized by placental vasculopathy and recurrent pregnancy loss.

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RECOMMENDATIONS

Who uses genetic services?

Genetic services are integral and intrinsic part of multidisciplinary health care system. All genetic services - laboratory and clinical should be standardized, accredited and use a system of quality control.

Users of genetic services are:

- couples with a child with a possible birth defect, inborn error of metabolism or neuromuscular disorder,
- couples who have experienced spontaneous abortions or a stillbirth and who wish to have prenatal diagnostic tests
- couples that have a child with congenital anomalies, an inborn error of metabolism or neuromuscular disorder and who wish to have prenatal tests in a subsequent pregnancy
- consanguineous marriages/partnerships
- patients with a suspicion of having FMF or with atypical manifestation of FMF
- patients with genetically confirmed diagnosis of FMF and family members for prognosis of complications, genetic risk calculation, and determination of carrier status
- individuals and families suspected of hereditary predisposition to cancer
- individuals exposed to potentially harmful physical, chemical or biological factors in pre-, peri- and post-conception (pregnant women) periods, including cancer survivors
- individuals seeking advice with the interpretation of results of commercial direct-to-consumer genetic testing

The gaps and recommendations are:

- ✓ Incorporation of genetic clinics in primary health care,
Development of workforce in the field of medical genetics: MDs, genetic counsellors, clinical geneticists, neonatologists, dysmorphologists and child neurologists,
- ✓ Provision of information and support to clinicians managing all types of genetic disorders,
- ✓ Development of health care and management facilities for most of hereditary disorders,
- ✓ Improving molecular and cytogenetic techniques that add accuracy to the diagnosis,
- ✓ Incorporation of more monogenic disorders into screening programmes,
- ✓ Introduction and extension of rapid prenatal diagnosis,
- ✓ Realization of newborn screening covering entire Armenia,
- ✓ Organisation of genetic management of complex diseases in collaboration with other medical disciplines,

- ✓ Identification of relatives at risk for hereditary disorders to provide support and genetic counseling including information concerning possible preventive and screening measures,
- ✓ Creation of nationwide register of hereditary disorders with clinical and genetic data,
- ✓ Use pharmacogenetic testing in collaboration with other medical disciplines,
- ✓ Application of universal approach for management, monitoring and genetic diagnostics of hereditary disorders using international guidelines such as those for FMF or DMD,
- ✓ Making available medicine of high quality (colchicine, etc) for every-day usage to avoid side effects,
- ✓ Education and adaptation of the society to meet the needs of patients with hereditary disorders.

Are high quality genetic services available and accessible?

Accessibility of services

- ✓ Prenatal screening services are available in all areas of the country, but certain procedures (amniocentesis, genetic testing) are only available in a few centers due to the professional and technical requirements of the procedure.
- ✓ Comprehensive prenatal testing (e.g., amniocentesis) and genetic counseling are only available in Yerevan, which may require travel from smaller communities or rural areas/frontier areas.
- ✓ Armenia has a mandatory state-administered prenatal screening program. All pregnant women must be offered ultrasound examination and blood and urine tests.
- ✓ Genetic testing and medical genetic consultation for newborns, children and adults are available only at the Center of Medical Genetics and Primary Health Care in Yerevan due to the relatively small number of geneticists.
- ✓ For few neuromuscular, metabolic and haematological disorders partial genetic diagnostics is available.
- ✓ Minimal residual disease assessment is not yet in routine clinical use.
- ✓ Genetic testing and genetic counselling of hereditary cancer syndromes is not recognized well and restricted to selected patients.

Quality of genetic services

- ✓ The lack of nationwide medial genetic services obviously influences the quality of health care services in Armenia.
- ✓ Professional standards and guidelines exist for prenatal screening and diagnosis, but not for genetic counselling and genetic testing.
- ✓ Genetic testing is performed using certificated test-systems with high quality control.
- ✓ Only clinical diagnosis of FMF is performed according to the clinical

questionnaire based on international protocols, and genetic counseling of FMF patients and families is based on the clinical and genetic investigations.

✓ The professional experience and information is not sufficient for the clinical diagnosis of all other genetic and hereditary disorders that are diagnosed by genetic testing.

Financial access to genetic services

✓ Newer genetic technologies, especially for rare disorders, are not covered

✓ Prenatal genetic counselling is not mandatory when required.

✓ The national newborn screening program covers all expenses for PKU and hypothyroidism.

✓ The diagnostics as well as care and therapies of all genetic and hereditary disorders remain at patient's personal expenses.

What genetic service delivery or policy issues do hereditary disorders highlight?

The delivery of genetic services dealing with medical testing and examination, recording and access of medical records should be a matter of a development of strong national policy regulating this specific field of medical activity.

Genetic counselling is a process of communication between genetic professionals and patients, with the goal of providing individuals and families with information on the relevant aspects of their genetic health, available testing and management options, and support as they move towards understanding and incorporating this information into their daily lives. On one hand, the principles of voluntary and informed decision making, nondirective and non-coercive counseling, and protection of client's confidentiality and privacy are central to the philosophy of genetic counselling and genetic testing, and should be strongly respected by each health care center providing such services. On the other hand, people considering genetic counselling and genetic testing must understand that their test results, as part of medical testing, may become known to other people or organizations that could have legitimate, legal access to their medical records, such as insurance companies, state medical councils such as for army drafting. However, legal protections should be in place to prevent genetic discrimination, which would occur if insurance companies, employers, or society were to treat people differently because they have hereditary disorder or a gene mutation that increases their risk of a disease or because they have a strong family history of a disease.

Currently, there is no law in Armenia regarding genetic information which in line with issues discussed above should prohibit any discrimination based on genetic information. A person's genetic information is considered a specific kind of health information and has to be covered by special national legislative regulations that requires that health care providers and others with medical record access protect the privacy of personal health information, sets limits on the use and release of health records, and empowers people to control certain uses and sharing of their health-related information.

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