

Structre disorders of corpus callosum - Clinical features in children and adolescents

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Abstract

Corpus callosum is the largest commissure connecting two cerebral hemispheres and consists of more than 200 million nerve fibers, which appear to be primarily excitatory. Its development begins by the 10th gestational week and its maturation continues up to young adulthood. Structure disorders of corpus callosum can be caused by genetic and by environmental factors (fetal alcohol syndrome) and include agenesis of corpus callosum (complete or partial), hypoplasia and dysgenesis. Children and adolescents with corpus callosum disorders can have many different clinical features, such as hypotonia, poor motor coordination and vision and hearing deficits. Furthermore, they lack self-awareness, they have difficulty in social interactions, they don't recognize easily other people's feelings and thoughts and their speech prosody is impaired. Therapeutic applications are based on the successful collaboration of many different specialties and should take place as soon as possible in order to exploit neural plasticity.

Key Words: corpus callosum, agenesis of corpus callosum, clinical features, children and adolescents, neural plasticity, behavioral disorders

Anatomy and Embryology of Corpus Callosum

Corpus callosum is the largest connective structure (commissure), which connects the left and right sides of the brain allowing for communication between both hemispheres. Other interhemispheric commissures of the brain are the anterior commissure, the commissure of fornix, the hippocampal commissure and the posterior commissure. It is estimated that corpus callosum consists of more than 200 million axons-connections,

which can be either homotopic or heterotopic. It is worth underlying that the anterior commissure consists of only 50,000 connections. [1] Corpus callosum is also topographically organized, so that fibers, which connect a given cortical area, are adjacent (regional organization of corpus callosum). [2, 3]

An interesting explanation for callosal evolution is that it arose to facilitate long-distance integration within large brains. Across species, increases in cortical volume are positively correlated with increases in CC area and number of callosal fibers. However, the correlation is nonlinear and as a result, species with larger brains actually have proportionately reduced interhemispheric connectivity and depend more heavily on intrahemispheric processing. [4-7] Although there has been debate about whether the connections are primarily excitatory (integrating information across hemispheres) or inhibitory (allowing the hemispheres to inhibit each other to maximize independent function), they appear to be primarily excitatory. [8] What's more, neurons and neuronc networks have been found within corpus callosum. (Fig. 1, 2)

Much of what we know about the stages of callosal development comes from animal models.[9]Corpus callosum formation involves multiple steps, which include correct midline patterning, formation of telencephalic hemispheres, birth and specification of commissural neurons (callosal projections neurons) and axon guidance across the midline to their final target in the contralateral hemisphere. [10, 11] Midline glial structures (e.g. glial wedge, midline zipper glia, indusium griseum) play an important role in the axon guidance, providing a growth substrate and expressing guidance molecules. [12] The commissural axons from the cortex are attracted to the midline mainly by proteins, such as netrins or semaphorin-3, which are expressed by midline cells and act as axonal growth cone guidance molecules. More specifically, these proteins interact with specific receptors on the cell surface of neurons (e.g. netrin/DCC, netrin/UNC-40, sem-3/neuropilins) and as a result commissural axons cross the midline and project alongside it, without recrossing. [13-16] An expla-

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nation for the failure to recross is that midline cells also express repellent proteins, such as Slit proteins and WNT proteins. When axonal growth cones cross the midline, they lose responsiveness to netrin and semaphorin. At the same time they upregulate receptors that interact with repellent proteins (e.g. Slit/ROBO-1&2 receptors, WNT-RYK receptors) and in this way axons are repelled into the contralateral hemisphere. It is worth underlying that another member of ROBO receptors (ROBO-3) is upregulated during growth of commissural axons and facilitates migration toward the midline and upon crossing it becomes downregulated. What's more, the UNC-5 receptor of netrin (as opposed to UNC-40 and DCC receptors) has a repellent migratory response to netrin binding and a similar effect to the Slit/ROBO system. [17-19] Several other molecules, such as cell adhesion molecules, laminins, fibroblast growth factor receptor1/ glial fibrillary acidic protein (Fgfr1/Gfap pathway) and specific transcriptional factors (e.g. Nfia, Nfib) are essential for the callosal formation. [20, 21] All these reflect the complexity of the multiple stages of callosal development.

Nerve fibers begin to cross the midline during the 10th gestational week, forming first the genu and the body (the central part of corpus callosum). The subsequent growth progresses bidirectionally (both anterior and posterior) throughout pregnancy. [7, 22] Full maturation and myelination of callosal fibers continue throughout childhood and adolescence until young adulthood. [23, 24] By 11 years both the anterior and posterior corpus callosum have reached 90% of their maximum fiber directionality and by 20 years they have 90% of their maximum external axonal structures. [24, 25]

Disorders of Corpus Callosum

1. Types

Structure disorders of corpus callosum include:

- complete absence (agenesis) of corpus callosum
- absence of some parts of corpus callosum (partial agenesis or hypogenesis); the absence must be evident from birth and not be representative of a degenerative condition.
- hypoplasia of corpus callosum: corpus callosum is fully formed, but is thinner than expected for age and sex of the individual. (Fig. 3)
- dysgenesis (malformation) of corpus callosum [16]

These structure disorders are often associated with other anomalies of CNS, such as Arnold-Chiari malformation, abnormal development of cerebellum and medulla oblongata, schizencephaly, myelomeningocele, encephalocele and cortical architectural disarray (heterotopic or ectopic neurons, polymicrogyria, reduction in number of Van Economo neurons). The topography and extent of these associated malformations are considered responsible for the heterogeneity of clinical symptoms and ultimate neurological prognosis. [26-28]

MRI is considered to be the most accurate and reliable diagnostic technology in detecting callosal disorders. Callosal microstructure is primarily studied via histology and dMRI. [29] One particular model of dMRI data, the diffusion tensor imaging (dTl) is now well established. A useful parameter of dTI is fractional anisotropy (FA), which indexes the degree of directionality or axon alignment in a tissue sample and can reflect fiber density, axonal diameter and myelination in white matter. [7] Neuroimaging findings that can accompany disorders of the corpus callosum are the enlargement of the 3rd ventricle, the dilatation of the posterior aspect of the lateral ventricles (colpocephaly), the hypoplasia of the hippocampus, the absence or malformation of the cingulate gyrus, the presence of cysts in the encephalic parenchyma and often the presence of atypical fiber bundles (Probst Bundles) that run anterior to posterior just lateral to the interhemispheric fissure. [30] Prenatal diagnosis of complete callosal agenesis is feasible from the midtrimester onwards by expert sonography. Fetal MRI is recommended in order to reinforce a difficult sonographic diagnosis and exclude possible additional cerebral anomalies, which affect the outcome considerably. [31, 32]

2. Prevalence

The improvement of neuroimaging methods gives the possibility to detect more and more cases of callosal disorders. This has led recently to an increase in prevalence of structure disorders of corpus callosum. Results from a study utilizing the California birth defect registry from 1983 to 2003 had indicated an overall birth prevalence of callosal malformations as 1.8 per 10,000 live births.[33] However, more recent studies suggest that agenesis of corpus callosum occurs in at least 1 per 4,000 live births, while other imaging studies have demonstrated that 3–5% of individuals

assessed for neurodevelopmental disorders have structure disorders of corpus callosum. It has also been proved that disorders of corpus callosum are more frequent among males. This could be attributed to the great number of X-linked syndromes, which are associated with structural abnormalities of corpus callosum (see Table 1). [16, 34]

3. Pathogenesis

Many genetic and environmental factors can interfere with normal development of corpus callosum. The genetics of corpus callosum abnormalities in humans are variable and reflect the underlying complexity of callosal development. For approximately 30–45% of individuals with corpus callosum disorders, the cause is identifiable; ~10% have chromosomal anomalies (e.g. trisomy 13, 15, 18) and the remaining 20–35% have recognizable genetic syndromes. A combination of genetic mechanisms, including single-gene Mendelian mutations (autosomal or X-linked), single-gene sporadic (de novo) mutations and complex genetics (a mixture of inherited and sporadic mutations) may be involved in the aetiology of these syndromes (see Table 1). However, if we only consider individuals with complete agenesis of corpus callosum, then the percentage of patients with recognizable syndromes drops to 10–15%, and thus 75% of cases of complete agenesis of corpus callosum do not have an identified cause. [35, 36]

Moreover, it is important to note that environmental factors might contribute to corpus callosum disorders as well. While much less is known about these than the genetic factors we have reviewed above, one clear example of environmental influences on callosal development is provided by fetal alcohol syndrome (FAS). [37] During the first trimester of pregnancy, alcohol interferes with the migration and organization of brain cells and can create structural deformities or deficits within the brain (e.g. microcephaly, corpus callosum agenesis, cerebellar hypoplasia). The incidence of corpus callosum agenesis in FAS is approximately 7%, with an even higher incidence of other corpus callosum malformations. [38, 39] However, the influence of alcohol on corpus callosum is damaging even in adulthood; recent studies have indicated that prolonged alcohol use (e.g. Wernicke encephalopathy cases, Marchiafava-Bignami syndrome cases-Fig. 4) can cause significant atrophy of this commissure. [40]

Other possible environmental risk factors for corpus callosum disorders are increased maternal age (> 40 years), maternal infections and maternal nutritional deficiencies.[37]

Clinical Features

In general, clinical signs and symptoms in corpus callosum structure disorders vary widely and their severity depends strongly on the presence of other malformations of CNS. Children and adolescents with isolated corpus callosum disorders (without other associated brain anomalies) can exhibit any of the clinical features described below, but their global functioning and future prognosis are much better. [41] On the other hand, the comparison between complete and partial corpus callosum agenesis has revealed conflicting data, with multiple studies showing no difference in behavioural and medical outcomes between the two conditions, whereas one earlier study reported a worse outcome for children with complete corpus callosum agenesis. [42]

Children with callosal conditions experience motor impairments such as hypotonia, spasticity, poor motor coordination and cerebral palsy. [43] Epilepsy and seizures are more common in these children and adolescents, with the reported prevalence varying from 27 to 86% depending on the population studied. Researchers have also reported early sucking, chewing, and swallowing difficulties and esophageal reflux. Besides, developmental delays are quite common among children with callosal conditions, with the reported prevalence ranging from 60 to 80% of those studied. Some children may exhibit delays in achieving motor, language and cognitive milestones and often accomplish toilet training at a much later age than their typically developing siblings (experiencing enuresis either occasionally or frequently). [44-46] Researchers agree that it is difficult to predict developmental outcomes in these infants and children. [47]

Individuals with callosal problems often have sensory deficits or abnormalities, with vision issues being the most commonly reported. Specific vision problems include problems with depth perception, near- and far-sightedness, strabismus and nystagmus. Hearing deficits, both mild and profound, have also been reported, sometimes with atypical patterns over time. [48] More specifically, young girls and boys were initially

diagnosed with hearing and vision problems. After some years these children's vision and hearing abilities had matured to near-normal abilities. [49] Furthermore, many children (46-56%) have abnormal reactions to touch and pain; they were described to have excessive sensitivity to particular tactile sensations (e.g. touch) and an unexpectedly high tolerance to pain. This phenomenon can set children in danger, causing injuries (e.g. broken bones, burns) and illnesses (e.g. burst eardrums, appendicitis) that go undetected until much later than would be expected.[43]

In most cases, children and adolescents with callosal conditions have normal intelligence, but usually in the low to average range. [50] Despite normal IQ scores, they frequently exhibit cognitive abnormalities. More specifically, they have difficulties in integrating information from multiple sources (e.g. verbal and visual ones), complex reasoning, abstract thinking, problem solving and generalization (the ability to extrapolate from one case to others); their category fluency (the ability to list multiple items that belong to a semantic category) can also be impaired. Due to these difficulties children and adolescents with callosal disorders cannot plan and execute effectively multidimensional tasks and sometimes even daily activities (e.g. homework, paying bills). [16, 51, 52] As regards school performance, with the strong involvement of parents, these children complete successfully elementary school. However, the academic gap between them and their peers widens during middle and high school years. This could be attributed to heavier demands of higher education and also to the small decrease of IQ scores over time observed in these children. [53] Moreover, some of these children often have problems with maintaining attention and sitting still, they are easily distracted and experience difficulties in tasks which demand attention and concentration. These manifestations remind strongly of attention deficit hyperactivity disorder (ADHD). [43] At this point we should mention that adolescents for years diagnosed with ADHD, after neuroimaging control, were found to have structure disorders of corpus callosum (cases of callosal dysgenesis and ADHD, smaller rostrum and splenium). [54]

One of the most examined domains in patients with corpus callosum disorders is language. These patients have difficulties in the comprehension of idioms, proverbs, vocal prosody, facial expressions and gestures. Overall, they lack comprehension of non-literal

language. Impairments have also been reported in phonological processing and rhythming. Furthermore, they have a marked difficulty in sustaining conversation; they change topics without providing the listener the reason, start spontaneously a new conversation, make 'meaningless' comments, talk 'in clichés' and usually don't take perspective of others. [55, 56] Another noticeable characteristic of most individuals with callosal problems is the diminished comprehension of humor (especially certain types of more abstract humor, such as irony or word play) and also the impairment in the verbal expression of their emotional experience (alexithymia). [10, 57] Moreover, they often make grammatical and syntactical errors, can't understand easily the main point of a passage and use significantly fewer words denoting negative emotions (anger, sadness, depression). In addition, when they are asked to produce narratives, they tend to use present tense verbs and they also prefer the first person. [58]

One potential explanation for this evident linguistic weakness is the model, according to which the cerebral hemispheres are asymmetrically specialized, with generation of verbal expression, comprehension of literal language, syntax and semantics principally processed in the dominant (typically left) hemisphere. On the other hand, the non-dominant (right) hemisphere is responsible for non-literal language, affecting prosody and negative emotions. In this model, corpus callosum is the main path for coordinating syntactic and prosodic information and information about negative emotions must be transferred from the right hemisphere to the left in order to produce accurate verbal descriptions about stimuli that involve negative emotions. It is clear that callosal disorders greatly reduce capacity for transferring this complex information between the hemispheres. [59] As regards comprehension of humor, fMRI studies have found a number of structures that are involved, some bilaterally and some specifically in the right hemisphere. [60] According to these findings, in the absence of corpus callosum, neither hemisphere alone possesses an adequate comprehension of humor. It is also worth mentioning that some of the deficits seen in individuals with callosal disorders (diminished comprehension of humor, proverbs, prosody) are similar to deficits seen in right hemisphere damaged patients. [61]

Parents and educators describe children and ado-

lescents with callosal problems as happy and friendly, but sometimes immature for their age (e.g. they prefer interacting with younger children than with children of the same age) or even socially naïve. [62] Furthermore, they lack self-awareness and the ability to recognize their own limitations. More specifically, they presume that they can accomplish things that are not within their skill abilities (putting themselves in danger). These children can also tell incorrect or untrue stories (e.g. sceneries of television programs) but believe what they are saying is true. This is often construed as lying by parents, friends or educators and the consequence can be punishment. In addition, callosal disorders can lead to general deficits in social judgment and misinterpretation of social cues. These individuals usually lack awareness of others' thoughts and feelings, have poor personal insight, cannot harmonize their behaviour with social circumstances and as a result suffer social isolation. [43, 63] Besides, children and adolescents with callosal problems may be more successful in routine social interactions, but have marked difficulties in new situations, where creativity, flexibility and initiative taking are necessary. This feature reminds of autism or Asperger syndrome, but the basic difference is that children with callosal conditions don't frequently display the repetitive or restrictive behaviours (e.g., spinning, lack of interest in others) more commonly seen in children with autism. So, it is rare for these children to receive a formal diagnosis of autism. [64] However, there are reports of abnormal corpora callosa in children already diagnosed with autism. These abnormalities include reduced corpus callosum volume and reduced FA of fibers throughout the commissure and support callosal involvement in autism. [65]

Extreme emotional or behavioural disorders are rarely reported among children and adolescents with callosal disorders. However, conditions of lesser severity, such as depression, anxiety or rapid mood changes have been observed. [43] There are also structural similarities between callosal disorders and some psychiatric disorders. For example, several studies have found altered morphology of corpus callosum in adolescents with schizophrenia and children with bipolar disorder, including changes in size and shape, as well as microstructural changes in callosal regions that are revealed by dMRI. [66, 67] Moreover, maltreated children (and especially those with posttraumatic stress disorder), who underwent longitudinal MRI brain inves-

tigations, were found to have reduced FA, compared to their healthy subjects, in medial and posterior corpus, a region which contains interhemispheric projections from brain structures involved in circuits that mediate the processing of emotional stimuli and various memory functions- disturbances associated with a history of trauma. Size of total corpus callosum and its subregions (2, 4, 5, 6 and 7) was also smaller than in control subjects. The data suggest that male children are more vulnerable to these effects. [68, 69] In addition, reduced corpus callosum was found in women with repeated episodes of sexual abuse in childhood, especially at ages 9-10 years. These disorders usually co-exist with other brain malformations and prove that environmental factors can influence postnatal callosal development. [70]

Individuals with congenital absence of corpus callosum appear to be affected differently than those whose corpus callosum is severed (callosotomy) in an attempt to control seizures. More specifically, patients who undergo callosotomies often exhibit a 'disconnection syndrome', which involves the complete lack of interhemispheric transfer (IHT) and integration of sensory and motor information presented independently to each of the hemispheres. This leads to a marked deficiency in bimanually coordinated motor activity and can also cause anomia for objects held in the left hand. However, the behavioural consequences in their everyday life were surprisingly subtle. Overall, individuals with corpus callosum agenesis perform better on tasks related to interhemispheric integration. The relative importance of age is illustrated by the finding that patients with early callosotomy and children with absence of corpus callosum show little evidence of a disconnection syndrome in IHT tests, whereas adolescent and adult callosotomy patients show marked transfer deficits. [16, 71, 72] It is possible that children with a congenital absence of the corpus callosum may benefit from early neural plasticity, which allows alternate neural pathways to develop. A place for neural plasticity is now recognized even for adults, but it is much more limited in comparison to developing brains. [10]

Theurapeutic Interventions - Future Directions

Corps callosum disorders often co-exist with other brain anomalies. What's more, the prognosis is unpre-

dictable and different from patient to patient. Due to these facts there are no therapeutic interventions applicable to all individuals and every therapeutic decision should focus on each patient's needs, which evolve over time. [43] The effectiveness of therapy depends on the successful collaboration of many different specialists (pediatricians, special educators, geneticists, neurologists, psychologists, physical and speech therapists). It is estimated that ~60% of children with callosal problems receive one or more therapies (the most frequent are physical, speech and occupational therapy). [48] As these children develop into adulthood, a crucial question is whether they can live independently, as some of their clinical disorders (the inability to recognize their limitations, the high pain tolerance, telling untrue stories) raise concern for their physical safety or can even have legal implications. In addition, some families report that their children show no observable deficits, commenting that their children are 'asymptomatic' or 'perfectly normal'. However, as more children with callosal disorders are identified and assessed with sensitive standardized neuropsychological measures, a pattern of deficits in higher-order cognition and social skills becomes apparent. Besides, some clinical deficits appear only later in life, when academic and social challenges are greater. [73] The key is parents, educators and therapists to monitor the child closely (even if he or she seems to be initially asymptomatic) and to

identify the problems as soon as possible. In this way, intervention services can begin early, before the child falls too far behind academically or behavioural issues emerge. Moreover, an earlier intervention can take advantage of neural plasticity.

Unfortunately, disorders of corpus callosum are conditions that patients and their families must "learn to live with" rather than 'hope to recover from'. Research on stem cells may provide in future a more permanent rehabilitation of structural disorders of corpus callosum. In field of genetics the identification of more genetic causes could give useful information about the mode of inheritance. What's more, the correlation of the genetics could be a useful tool for informing families, understanding the pathophysiology of related co-existing conditions and developing individualized therapeutic strategies. In addition, the knowledge of the involved genes is a precondition for a possible application of gene therapy in future. It is also worth-underlying that the complex embryological development of corpus callosum renders it an ideal model for the study of development of other systems of organism too. Besides, the frequent existence of callosal problems in patients with neurological and psychiatric disorders (e.g. schizophrenia, bipolar disorder, ADHD, autism) may throw new light on the pathogenetic mechanisms of these situations.

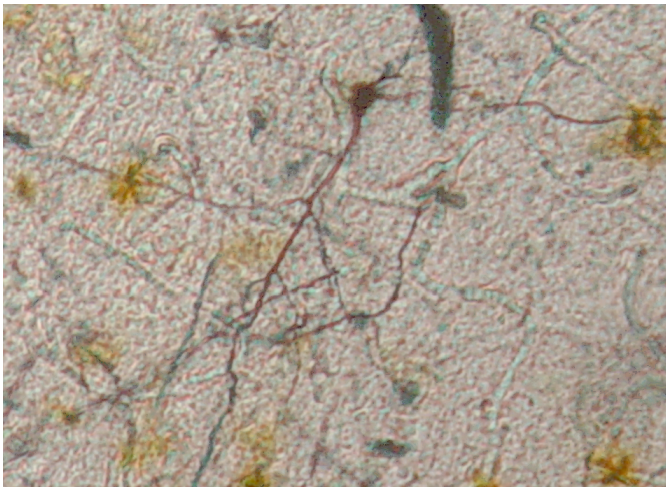


Figure 1: Neuronic networks within corpus callosum. 1st Neurological Departments, Aristotle University of Thessaloniki

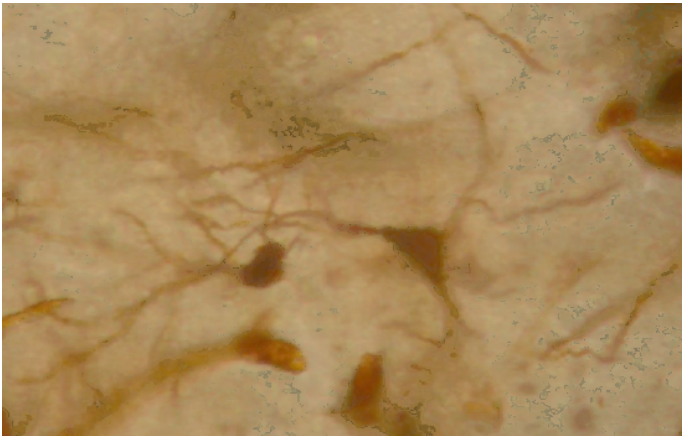


Figure 2: Scattered neurons within corpus callosum. 1st Neurological Department, Aristotle University of Thessaloniki



Figure 3: Hypoplasia of corpus callosum in an adult patient. 1st Neurological Department, Aristotle University of Thessaloniki

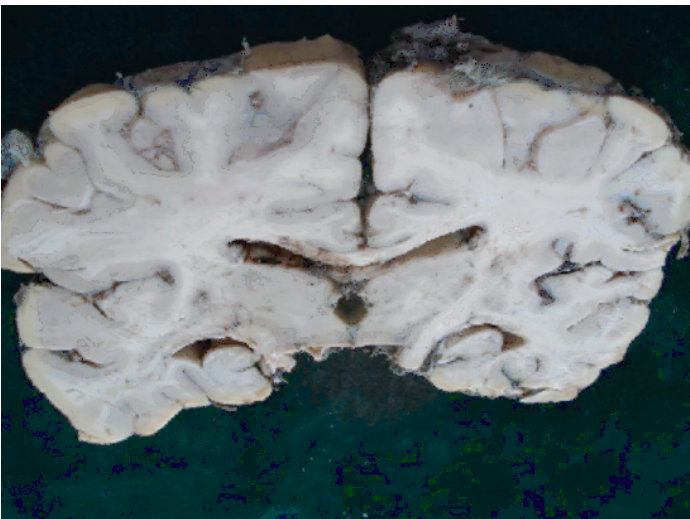


Figure 4: Corpus callosum fusion in a patient with Marchiafava-Bignami syndrome. This patient had upper limbs apraxia, visuospatial orientation disorders and mild mental retardation. 1st Neurological Department, Aristotle University of Thessaloniki

Πίνακας 1: Γενετικά σύνδρομα που συνδέονται με διαταραχές του μεσολοβίου

Σύνδρομο	Υπεύθυνο γονίδιο	Συνοδά ευρήματα
CRASH	LICAM gene (Xq28)	hydrocephalus, spasic paraplegia, mental retardation, adducted thumbs (74)
XLAG	ARX gene (Xp22 13)	lissencephaly, mental retardation, epilepsy, ambiguous genitalia (75)
Mowat-Wilson	ZFXH1B gene (2q22)	Hirschsprung disease, congenital heart disease, genitourinary anomalies, epilepsy (76)
Donnal-Barrow	LRP2 gene (2q23.3-31.1)	sensorineural hearing loss, vision impairment, congenital diaphragmatic hernia/omphalocele, heart defects (77)
Andermann (ή νόσος Charlevoix)	SLC12A6 gene (15q13-q14)	mixed motor and sensory neuropathy (78)
Acrocallosal	GLI3 gene (7p13)	mental retardation, facial dysmorphology, polydactyly (79)
Toriello-Carey	? gene (3q29, 6p25)	heart defects, hypotonia, mental retardation, postnatal growth delays, minor facial dysmorphisms (80)
Aicardi	? gene (Xp22)	mental retardation, infantile spasms (81)
Wolf-Hirschhorn	απώλεια γονιδίων από το 4p16.3	microcephaly, seizures, growth retardation, muscular underdevelopment, skeletal anomalies, "Greek warrior helmet appearance" of the nose (82)
Menkes	ATP7A gene (Xq13.2-13.3)	disorder of copper metabolism, neurodegeneration, peculiar "kinky" hair. death< 3rd year of life (83)
Sotos	NSD1 gene (5q35)	physical overgrowth, cardiac anomalies, mental retardation, increased risk of tumors (84)
De Morsier	HESX1 gene (3p21.2-p21.1)	hypoplasia of septum pellucidum and optic chiasm, hypopituitarism (16)
Lujan-Fryns	MED12 gene (Xq13)	Marfanoid habitus, cardiac anomalies, behavioral abnormalities (85)
Opitz GBBB	? gene (22q11.2) MID1 gene (Xp22)	hypospadias, hypertelorism, dysplasia of trachea/larynx/esophagus (86)
Zellweger	12 PEX genes	vision impairment, liver dysfunction, episodes of hemorrhage, mental retardation (87)

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