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RESEARCH ARTICLE

AN OVERVIEW OF LESS KNOWN JACOBSEN SYNDROME

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Abstract

Jacobsen syndrome is catastrophic in 1 out of every 5 cases, with children usually dying within the first 2 years of life due to heart complications. Jacobsen syndrome is a contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11. The prevalence has been estimated at 1/100,000 births, with a female/male ratio 2:1. The most common clinical features include pre- and postnatal physical growth retardation, psychomotor retardation, and characteristic facial dysmorphism (skull deformities, hypertelorism, ptosis, coloboma, downslanting palpebral fissures, epicanthal folds, broad nasal bridge, short nose, v-shaped mouth, small ears, low set posteriorly rotated ears). Abnormal platelet function, thrombocytopenia or pancytopenia are usually present at birth. Patients commonly have malformations of the heart, kidney, gastrointestinal tract, genitalia, central nervous system and skeleton. Ocular, hearing, immunological and hormonal problems may be also present. The deletion size ranges from 07 to 20 Mb, with the proximal breakpoint within or telomeric to subband 11q 23.3 and the deletion extending usually to the telomere. The deletion is *de novo* in 85% of reported cases, and in 15% of cases it results from an unbalanced segregation of a familial balanced translocation or from other chromosome rearrangements. Diagnosis is based on clinical findings (intellectual deficit, facial dysmorphic features and thrombocytopenia) and confirmed by cytogenetics analysis.

Introduction:-

The syndrome was first identified by Danish geneticist Petrea Jacobsen in 1973 and was named after her. She discovered Jacobsen syndrome in a family where multiple people had the disorder. She discovered that the affected children had unbalanced translocation between chromosome 11 and 21 which they had inherited from one of their parents who had balanced translocation. Since then, only 200 cases have been reported of Jacobsen syndrome in medical literature. Jacobsen syndrome is a condition caused by a loss of genetic material from chromosome 11. Because this deletion occurs at the end (terminus) of the long (q) arm of chromosome 11, Jacobsen syndrome is also known as 11q terminal deletion disorder. The signs of Jacobsen syndrome vary considerably. Most affected individuals have delayed development, including the development of speech and motor skills (such as sitting, standing, and walking). Most also have cognitive impairment and learning difficulties. Behavioral problems have been reported, including compulsive behavior (such as shredding paper), a short attention span, and easy distractibility. Many people with Jacobsen syndrome have been diagnosed with attention-deficit/hyperactivity

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disorder (ADHD). Jacobsen syndrome is also associated with an increased likelihood of autism spectrum disorders, which are characterized by impaired communication and socialization skills.

Jacobsen syndrome is also characterized by distinctive facial features. These include small and low-set ears, widely set eyes (hypertelorism) with droopy eyelids (ptosis), skin folds covering the inner corner of the eyes (epicanthal folds), a broad nasal bridge, downturned corners of the mouth, a thin upper lip, and a small lower jaw. Affected individuals often have a large head size (macrocephaly) and a skull abnormality called trigonocephaly, which gives the forehead a pointed appearance.

More than 90 percent of people with Jacobsen syndrome have a bleeding disorder called Paris-Trousseau syndrome. This condition causes a lifelong risk of abnormal bleeding and easy bruising. Paris-Trousseau syndrome is a disorder of platelets, which are blood cells that are necessary for blood clotting.

Other features of Jacobsen syndrome can include heart defects, feeding difficulties in infancy, short stature, frequent ear and sinus infections, and skeletal abnormalities. The disorder can also affect the digestive system, kidneys, and genitalia. The life expectancy of people with Jacobsen syndrome is unknown, although affected individuals have lived into adulthood.

Definition

Jacobsen syndrome is rare chromosomal disorder resulting from deletion of genes from chromosomes 11. It is a congenital disorder. Since the deletion takes place on the q arm of chromosome 11, it is also called 11q terminal deletion disorder. The deletion may range from 5 million to 16 million deleted DNA base pairs. The severity of symptoms depends on the number of deletions; the more deletions there are, the more severe the symptoms are likely to be.

People with Jacobsen syndrome have serious intellectual disabilities, dysmorphic features, delayed development and a variety of physical problems including heart defects. Research shows that almost 88.5% of people with Jacobsen syndrome have a bleeding disorder called Paris-Trousseau syndrome.

Causes

Jacobsen syndrome is caused by a deletion of genetic material at the end of the long (q) arm of chromosome 11. The size of the deletion varies among affected individuals, with most affected people missing 5 million to 16 million DNA building blocks. In almost all affected people, the deletion includes the tip of chromosome 11. Larger deletions tend to cause more severe signs and symptoms than smaller deletions.

The features of Jacobsen syndrome are likely related to the loss of multiple genes on chromosome 11. Depending on its size, the deleted region can contain from about 170 to more than 340 genes. Many of these genes have not been well characterized. However, genes in this region appear to be critical for the normal development of many parts of the body, including the brain, facial features, and heart. Interstitial deletions in this region and terminal deletions less than 7Mb can cause a "partial Jacobsen syndrome" phenotype. In a minority of cases the breakpoint is at the FRA11B fragile site. There are a few reported cases of mosaicism for the deletion, which may lessen the severity of the clinical phenotype.

Inheritence

Most cases of Jacobsen syndrome are not inherited. They result from a chromosomal deletion that occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family, although they can pass the chromosome deletion to their children.

Between 5 and 10 percent of people with Jacobsen syndrome inherit the chromosome abnormality from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which a segment from chromosome 11 has traded places with a segment from another chromosome. In a balanced translocation, no genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation.

Children who inherit an unbalanced translocation can have a chromosomal rearrangement with some missing genetic material and some extra genetic material. Individuals with Jacobsen syndrome who inherit an unbalanced translocation are missing genetic material from the end of the long arm of chromosome 11 and have extra genetic material from another chromosome. These chromosomal changes result in the health problems characteristic of this disorder.

Epidemiology

Whilst prevalence of Jacobsen syndrome is unknown, the birth prevalence has been suggested at 1/50,000-100,000 in the United States, with a female/male ratio of 2:1.

Clinical Description

Patients with JS are born at term in more than 60% cases, premature birth occurs in about 30% of cases, while delivery is post term in less than 10% of cases. Complications at delivery occur in 46% of cases: abnormal fetal presentation, premature rupture of the membranes, cephalopelvic disproportion. Delivery is spontaneous in about 65% of cases, whereas Cesarean section is performed in 35% of cases. Birth weight is normal (between the 10^{th} and the 90^{th} percentile) in 60% of babies, below the 10^{th} percentile in 37%, while 3% of children have a birth weight above the 90^{th} percentile. Mean maternal age is 27 years, mean paternal age is 30 years. During the neonatal period, most JS children have prolonged hospitalizations, due most commonly to a combination of feeding difficulties, cardiac problems, and/or bleeding problems. About 20% of children die during the first two years of life, most commonly related to complications from congenital heart disease, and less commonly from bleeding. For patients who survive the neonatal period and infancy, the life expectancy is unknown, Dr. Jacobsen's index case is 45 years old and is living in a group home.

There is a wide spectrum of severity of the clinical phenotype. Half of the patients are diagnosed by age one year of life, usually those with the more obvious clinical features of the disorder, while children with milder features may be diagnosed at an older age.

Physical growth delay

Height is below the 10^{th} percentile in 75% of cases and in the normal range in 25%. Weight is below the 10^{th} percentile in 58%, normal in 34% and above the 90^{th} percentile in 8% of cases. Head circumference is below the 10^{th} percentile in 26%, normal in 53% and above the 90^{th} percentile in 21% of cases.

Psychomotor developmental delay

Mental development is normal or borderline in less than 3% of cases, mild to severe mental retardation is observed in 97% of cases. The degree of neurocognitive deficiency is strongly associated with the size of the deletion [3, 10]. Children manifest behavioral problems, most frequently attention deficit/hyperactivity disorder, while more severe psychiatric disorders such as schizophrenia, or bipolar affective disorder have been reported rarely [11, 12]. Seizures have been reported infrequently.

Dysmorphic features and minor malformations

Typical features are: skull deformities (macrocrania, high prominent forehead, facial asymmetry, trigonocephaly), ocular hypertelorism, downslanting palpebral fissures, strabismus, palpebral ptosis, sparse eyebrows, epicanthal folds, eyelid coloboma, ectropion, iris coloboma, cataract, tortuosity of retinal vessels, flat or prominent nasal bridge, short nose, anteverted nares, prominent columella, broad nasal bridge, small ears, low set posteriorly rotated ears, malformed external ears, hypoplastic lobus, long philtrum, flat philtrum, v-shaped mouth, thin upper lip, retrognathia, and other less frequently observed. Hands show cutaneous syndactyly, flat finger pads with fetal tubercule, thin fingers, large 1^{st} interphalangeal joints, hypoplastic hypotenar regions, abnormal palmar creases, hypoplastic thenar regions. Feet are stubby and flat, with large and long first toe, clynodactylous toes, brachydactyly, syndactyly of the 2^{nd} and 3^{rd} toes, crowded toes. The main features of JS, based on 35 patients that we have assessed, are listed in Table 1. In some reports the presence of trigonocephaly has been described as a common feature. Trigonocephaly is an abnormality of the skull shape characterized by a triangular appearance of the forehead when the head is viewed from above. It is often associated with premature closure of the metopic suture. The presence of trigonocephaly gives the patient a very characteristic facial appearance that raises the possibility of the diagnosis, however in our experience the frequency of trigonocephaly in JS patients seems less high than previously reported (< 30%). The prevalence of trigonocephaly at birth is reported as 67:1,000,000 in the general

population; in a series of 25 children selected for the presence of syndromic and non syndromic trigonocephaly, two out of seven syndromic cases (28.5%) were JS patients

Visceral malformations

Congenital heart malformations occur in 56% of cases. Most of these require medications and/or surgical repair. Cardiac malformations were reported in 95% of deceased children. The most frequent heart defects (2/3 of patients that have congenital heart defects) are ventricular septal defects, or left heart obstructive malformations: abnormalities of aortic or mitral valves, coartation of the aorta, Shone's complex, or hypoplastic left heart syndrome. Hypoplastic left heart syndrome, a rare and severe condition that occurs in about 1/5000 infants, is observed in 5% of JS children. The other one third of patients with heart defects have a wide spectrum of most of the common heart defects that occur in the general population of patients with congenital heart disease . Gastrointestinal tract malformations occur in 18% of reported cases, and in 25% the patients we have assessed, including pyloric stenosis, anal abnormalities (atresia or stenosis, or anteriorized anus), and less frequently, duodenal atresia, annular pancreas, or gut malrotation. Functional abnormalities of the gastrointestinal tract also occur frequently, including feeding difficulties in the neonatal period and chronic constipation, requiring medication, beyond the newborn period. Among JS patients who were analyzed with cerebral ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) scanning or by autopsy, 65% had some kind of structural abnormality of the brain: enlarged ventricles with or without spina bifida, cerebral atrophy, agenesis of corpus callosum, pachygiria. Supratentorial abnormalities of the white matter are interpreted as due to delay of myelinization, or partial loss of astrocytes, rather than a process of demyelinization.

Urinary system malformations are observed in 13% of JS children: unilateral kidney dysplasia, double urethers, double kidney district, hydronephrosis, multicystic kidneys. Cryptorchidism is observed in 36% of males in published reports, and in about 60% our series. Inguinal hernias are observed in 15% of children.

In addition to craniosynostosis, 14% of children display some skeletal abnormality including spina bifida occulta, vertebral body anomalies, chest anomalies, abnormal number of ribs, micromelia, hexadactyly. Orthopedics abnormalities are observed in 19% of children including hip dislocation, scoliosis, flat feet, or clubbed feet.

Hematological, hormonal and immunological aspects

Most patients with the JS are born with either thrombocytopenia or pancytopenia. More recently a definite platelet disorder, the Paris-Trousseau syndrome, has been reported in patients with JS. This platelet abnormality is highly penetrant in JS, affecting at least 88.5% of cases, and it has been suggested that the platelet abnormality in JS and the Paris-Trousseau syndrome are the same condition. Paris-Trousseau syndrome is characterized by neonatal thrombocytopenia which may resolve over time, and platelet dysfunction (which is usually persistent). In peripheral blood there are two different types of abnormal platelets: giant platelets and platelets with giant alpha granules. Platelets showing giant alpha granules are a minority, but their amount is variable in different patients and in the same patient at different times. Immunocytochemical and ultrastructural studies demonstrated that the giant granules arise by abnormal fusion of smaller organelles These abnormally fused alpha granules may be due to a failure of the alpha granules to release their contents that are required for coagulation, under normal physiologic conditions. In the bone marrow there is an increased number of small megakaryocytes (micromegakaryocytes), and delayed maturation of megakaryocytes . It has been observed that in JS the platelets have a reduced number of serotonin adenine rich dense bodies, suggesting a storage pool deficit

Growth hormone (IGF-1) and thyroid-stimulating hormone (TSH) deficiency have been reported in patients with JS

Although JS infants show recurrent otitis and sinusitis, deficit of cellular or humoral immunity with low IgM and IgA has been reported only occasionally. Cutaneous eczema is observed in 22% of JS children, but there is no obvious increased risk for severe allergic reaction to food or medications.

Malignancies

Somatic acquired chromosome deletions of 11q overlapping the JS region have been demonstrated in a variety of malignancies of adulthood, frequently associated with aggressive progression of the disease and poor prognosis. It might be expected, therefore, that constitutional deletions of 11q regions result in an increased risk for developing neoplastic lesions and/or poor prognosis. There is no evidence of increased risk of malignancies in JS patients from the literature, but clinical reports have concerned mainly JS children, and little is known about their outcome in older ages. Better clinical management of JS children leading to longer survivals could reveal an increased risk for

the development of malignancies in JS patients in adulthood. Alternatively, it is possible that deletion of 11q terminal region is causally related only with an aggressive progression of cancer rather than with an increased risk of neoplastic transformation and cancer onset.

Etiology

In Jacobsen Syndrome the chromosome aberration is usually a over again from the beginning pure terminal deletion (85% of cases). Less frequently, unbalanced translocations result from segregation of a familial balanced translocation, as in the original report by Jacobsen. Alternatively, partial deletion of chromosome 11q may result from unbalanced translocations occurring de novo, or from other chromosomal rearrangements such as ring chromosomes or recombination of a parental pericentric inversion. In these cases 11q deletion is complicated by additional imbalances.

Jones et al. reported that in two JS patients the expansion of the CCG repeat at the FRA11B, with or without cytogenetic expression of the fragile site, was at the origin of the 11qter deletion. In both cases the deleted chromosome was maternal. It is hypothesized that hypermethylation of the expanded (CCG)n triplets on chromosome 11 could delay DNA replication of this fragile site, resulting in a break and/or impaired DNA replication.

Only a minority of cases of JS (10%) are related to amplification of the CCG triplet at the FRA11B folate sensitive fragile site, and individuals with the FRA11B rarely have children with JS. Therefore, the presence of the FRA11B fragile site may increase the risk of having JS offspring, but not necessarily result in a child with an 11q deletion. Most 11q deletions occur distally to the FRA11B, and it is possible that expansion at other fragile sites may be responsible for distal 11q deletions. However, to date no other fragile sites have been identified in the parents of JS patients with deletions whose breakpoints map telomeric to the FRA11B fragile site.

Alternatively, smaller deletions are likely to occur by other mechanisms: it has been shown that chromosome recombinations can be mediated by low copy repeats (LCR), palindromic AT-rich repeats (PATRRs), olfactory receptor gene clusters (ORGC). Taken together, there are likely to be multiple mechanisms that lead to the generation of 11q deletions.

In JS patients the origin of the deleted chromosome is more likely to be maternal for breakpoints occurring proximally to D11S924 (band 11q23.3), while there is a paternal bias when the breakpoint is more distal. It is likely that imprinting is involved in the mechanisms of (CCG)n expansion and methylation.

Genotype/phenotype correlation:

Although the patients with the largest deletions usually show the most severe phenotype, this can vary between patients. For example, as described above, almost all patients have Paris-Trousseau syndrome, but only 56% of patients have a congenital heart defect, independent of the size of their deletion. The minimal region for expressing the JS phenotype spans about 14 Mb.

Features of JS, resulting in a partial expression of the JS phenotype, have been observed in patients with very small terminal deletions and in cases of interstitial deletions spanning within the JS region.

A terminal deletion of about 5 Mb, with a breakpoint at 129.5 Mb, was reported in three patients from a kindred, with some facial features of JS, with or without mental retardation, and without cardiac malformation and thrombocytopenia.

Some facial features of JS, heart defect and the Paris-Trousseau thrombocytopenia, have been observed in a child with an interstitial deletion of about 10 Mb spanning between 120.0/121.5 and 129.7/130.6, thus almost entirely proximal to that of previous report .

Two further patients with interstitial deletions have been reported to show some features of JS, but not the distinct and recognizable facial aspect. The region spanning between 120 and 130.6 Mb is probably the most important for the expression of the phenotype.

Attempts to correlate the clinical findings to the extent of the deletion, complicated by incomplete penetrance for specific phenotypes as described above, has nonetheless provided the following results: Trigonocephaly and skin syndactyly have been localized to a region defined between D11S933 (124 Mb) and D11S912 (128 Mb) Phillips et refined the critical region for hypoplastic left heart and trigonocephaly to a region distal to D11S1351 [40], mapping to 127.5–127.7 Mb, according to UCSC database. Grossfeld mapped the Paris-Trousseau platelet disorder, cryptorchidism, pyloric stenosis, and mental retardation to the 6.8 Mb telomeric region spanning from D11S1351 (127.5 Mb). The region spanning from D11S707 (125.7 Mb) to the telomere is associated with cardiac defects , but more than one gene might be involved in cardiac malformation . The region distal to D11S1299 (119 Mb) is related to ocular coloboma. Genotype – phenotype correlation has been attempted also in reports concerning patients where 11q terminal deletions are due to the segregation of unbalanced translocations. These cases may allow further refinement of the phenotype mapping, however a possible role of the associated duplications must be considered.

Relevant genes and loci

11q23 qter is a gene rich region: it includes 342 genes, 174 of which have been localized to 11q24.1 qter, the minimal region for expressing the JS, of about 14 Mb. The FLI-1 gene maps to chromosome subband 11q24, in the region deleted in JS patients. It is a proto-oncogene belonging to the ETS family and interacting with a number of genes involved in vasculogenesis, hematopoiesis and intercellular adhesion. There is *in vivo* and *in vitro* evidence that FLI1 plays a fundamental role in megakaryocytes differentiation and that heterozygous loss of the FLI-1 gene is associated with dysmegakaryocytopoiesis and the Paris-Tousseau trombocytopenia in JS. Furthermore, in vitro induced over-expression of the *FLI-1* gene in patient (*i.e.* patients that are haplo-insufficient for FLI-1) CD34+ cells, restores normal megakaryopoiesis, however other genes in distal 11q may also contribute to this disorder. The *BARX 2* gene maps to chromosome 11q, within the minimal deleted region for JS. It has four exons and encodes a homeobox protein. Its murine homologue *barx2* is expressed in the development of neural and craniofacial structures. The BARX 2 gene, because of its location and its expression pattern, is a possible candidate gene for the development of facial dysmorphism and/or craniosynostosis in JS. However no mutation in the BARX2 gene has been detected in nine patients with isolated trigonocephaly. JAM3 has been considered a candidate gene for hypoplastic left heart and trigonocephaly. It is a member of the junction adhesion molecules family; the gene maps within the critical region for hypoplastic left heart (HLH) that is a 9 Mb region in the long arm of chromosome 11 distal to D11S1351 (127.5 Mb). Analysis of the JAM3 gene in thirty-three patients with isolated HLH, failed to demonstrate any mutation; this would suggest that other genes are mainly involved in this malformation. Tyson et al. , suggested that a critical region for the conotruncal heart defect may lie within a region spanning between 129.03 and 130.6 Mb, which bears ADAMTS8, a gene involved in angiogenesis.

B3GAT1, a beta-1–3-glycoronyltransferase gene located in 11q25 at 133.77 Mb, is expressed in the brain. Knock out mice show impaired synaptic plasticity and learning disabilities. This gene could be involved in bipolar disorder observed in some JS patients [12].BSX, an evolutionarily highly conserved homeobox gene, expressed during early brain development and mapping in 122.3 Mb has been proposed as a candidate gene for global cognitive development, while NRGN (neurogranin), a gene involved in synapse plasticity and long-term potentiation and mapping in 124.1 Mb has been suggested to contribute to the auditory attention deficit. Abnormalities of the white matter appear to map between 124.6 Mb, and 129.03 and hypothetical candidate genes include FEZ1, involved in axonal outgrowth, and RICS, highly expressed in developing brain.

KCNJ 1, a potassium channel, and ADAMTS15, a zinc-dependent proteases expressed in fetal liver and kidney may be related to kidney malformations.

TECTA, a gene coding for a non collagenous component of the tectorial membrane of the inner ear, may be involved in neurosensorial deafness.

A number of tumor related genes map in 11q distal region: *EST1, CHK1, BARX2, OPCML, FLI-1*, their role in tumor development and progression in JS is still unknown

Conclusion:-

Jacobsen syndrome is a rare chromosomal disorder resulting from deletion of genes from chromosome 11 that includes band 11q24.1. It is a congenital disorder. Since the deletion takes place on the q arm of chromosome 11, it is also called 11q terminal deletion disorder. The deletion may range from 5 million to 16 million deleted DNA base

pairs. The severity of symptoms depends on the number of deletions; the more deletions there are, the more severe the symptoms are likely to be. People with Jacobsen syndrome have serious intellectual disabilities, dimorphic, delayed development and a variety of physical problems including heart defects. Research shows that almost 88.5% of people with Jacobsen syndrome have a bleeding disorder called Paris-Trousseau syndrome.

It is also prudent that the ENS be viewed in the light of emergent parent child relationships. In the past few years, parent child relationship paradigms have changed and duty towards parents is not looked at as a moral compulsion while parenting is often viewed as something everyone has to do and after a certain stage children need to be set free. Children and parents have always had their generation gaps and with a further widening of these gaps in the modern era, the emotional bonding between parent and child has reduced leading to probably a lower occurrence of the ENS phenomenon.

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