

Beckwith-Wiedemann Syndrome

The Beckwith-Wiedemann syndrome (BWS) is the most common and the best-known congenital overgrowth syndrome. It was named after Beckwith who in 1963 described three unrelated patients with exomphalos, hyperplasia of the kidneys and pancreas, and adrenal cytomegaly. Wiedemann in 1964 reported a familial form of omphalocele with macroglossia. The incidence is estimated to be about 1 in 13,700 births.

GENETICS/BASIC DEFECTS

1. Genetics of BWS: complex
 - a. Pedigree data
 - i. Sporadic (85%)
 - ii. Familial (15%): autosomal dominant inheritance with variable expressivity, incomplete penetrance, and preferential maternal transmission
 - b. Karyotypic data
 - i. Chromosome rearrangements influenced by the parent of origin (2%)
 - a) Paternally derived 11p15.5 duplications exhibiting atypical clinical features as well as a significant risk of developmental delay
 - b) Maternally derived translocations and inversions exhibiting typical features of BWS
 - ii. Normal karyotype (98%)
 - c. Molecular data: BWS is caused by alterations in growth regulatory genes on chromosome region 11p15.5, which is subjected to genomic imprinting (an epigenetic mechanism in which gene expression is altered according to the parental origin of the allele)
2. Pathogenesis
 - a. Imprinted genes have been implicated in the pathogenesis of both familial and sporadic BWS
 - b. A subgroup of BWS patients has loss of methylation at a differentially methylated region (KvDMR1) within the *KCNQ1* gene centromeric to the *IGF2* and *H19* genes
 - c. Maternally expressed 11p genes
 - i. *P57^{KIP2}* (also known as *CDKN1C*, a cation-independent cyclase): a candidate for a maternally expressed growth inhibitory gene in BWS
 - a) Germline mutations detected in >40% of familial cases
 - b) Mutations infrequent (<5%) in sporadic cases
 - ii. *H19*: a maternally expressed gene encoding a biologically active nontranslated mRNA that may function as a tumor suppressor. Deletion of *H19* or transposition from its usual position relative to *IGF2* disrupts normal imprinting
 - iii. *KCNQ1* (also known as *KvLQT1*): serves as an imprinting center, disruption of which could affect transcription and DNA replication through an effect on chromatin structure
 - d. Paternally expressed 11p genes
 - i. *IGF2* (the gene for insulin-like growth factor-2): a paternally expressed and maternally imprinted embryonic growth factor. Many sporadic cases show loss of imprinting of *IGF2* resulting in biallelic expression
 - ii. *KCNQ1OT1* gene (also known as *LIT1*): the unmethylated paternal allele of KvDMR1 permits transcription of the antisense transcript *KCNQ1OT1* and silencing of the *KCNQ1* and *CDKN1C* genes
 - e. Effect of multiple genes: combination of increased expression of paternally expressed growth promoter genes such as *IGF2* and loss of maternally expressed growth suppressor genes in some patients with paternal uniparental disomy of 11p15
 - f. Uniparental disomy (mosaic paternal isodisomy) for the band 11p15.5 (10–20% of sporadic cases)
 - i. Two paternally derived copies of chromosome 11p15 and no maternal contribution for that chromosome region
 - ii. Resulting from postzygotic mitotic recombination and mosaic paternal isodisomy
 - iii. All patients with uniparental disomy exhibit somatic mosaicism

CLINICAL FEATURES

1. Variable phenotypic expression
2. Prenatal and postnatal overgrowth (gigantism) (cardinal feature)
 - a. Large or above normal size baby at birth
 - b. Eventual somatic gigantism in most cases
 - c. Advanced bone age
 - d. Hemihyperplasia or hemihypertrophy (13%)
3. Performance
 - a. Varying intelligence
 - i. Normal
 - ii. Mild-moderate mental retardation from undetected hypoglycemic episodes during infancy
 - b. Seizures in some cases
4. Craniofacial features
 - a. Macroglossia (cardinal feature)
 - i. Chronic alveolar hypoventilation
 - ii. Anterior open bite
 - b. Ear-lobe grooves or indented ear lesions on the posterior rim of the helix or concha
 - c. Nevus flammeus
 - d. Midfacial hypoplasia
 - e. Prominent occiput
5. Abdominal wall defect
 - a. Omphalocele (cardinal feature)
 - b. Umbilical hernia
 - c. Diastasis recti

6. Gastrointestinal anomalies
 - a. Malrotation anomalies
 - b. Dome-shaped defect of the diaphragm
7. Visceromegaly
 - a. Hepatomegaly (frequent)
 - b. Nephromegaly (frequent)
 - c. Cardiomegaly
 - d. Occasional clitoromegaly
 - e. Hyperplastic pancreas, bladder, uterus, and thymus
8. Neoplasms (7.5%)
 - a. Benign tumors
 - i. Adrenal adenoma
 - ii. Carcinoid tumor
 - iii. Fibroadenoma
 - iv. Fibrous hamartoma
 - v. Ganglioneuroma
 - vi. Myxoma
 - b. Malignant tumors
 - i. Wilms tumor (most frequent)
 - ii. Adrenocortical carcinoma
 - iii. Hepatocellular carcinoma
 - iv. Glioblastoma
 - v. Neuroblastoma
 - vi. Rhabdomyosarcoma
 - vii. Malignant lymphoma
 - viii. Pancreatoblastoma
 - ix. Teratoma
9. Additional features
 - a. Polyhydramnios
 - b. Prematurity
 - c. Enlarged placenta
 - d. Hemangioma
 - e. Other renal anomalies
 - i. Medullary dysplasia
 - ii. Duplicated collecting system
 - iii. Nephrocalcinosis
 - iv. Medullary sponge kidney
 - v. Cystic changes
 - vi. Diverticula
10. Adult phenotype
 - a. Hemihyperplasia
 - b. Prominent jaw
 - c. Enlarge tongue
 - d. Ear creases and pits
 - e. Enlarged kidneys and other abdominal organs
 - f. Normal height
6. Echocardiography for suspected cardiac abnormality
7. Chromosome analysis (high resolution and FISH studies)
 - a. Normal chromosomes in most patients
 - b. Chromosome abnormalities involving 11p15 in $\leq 1\%$ of cases
 - i. Paternally derived 11p15 duplication
 - ii. Maternally derived translocations and inversions
8. Molecular analysis
 - a. Paternal uniparental disomy (UPD) of 11p15 in multiple tissues (10–20%)
 - i. Restriction fragment length polymorphism (RFLP) analysis of multiple 11p15 loci
 - ii. Methylation studies of multiple imprinted genes on 11p15
 - b. Mutation analysis: *P57^{KIP2}* (5–10%) (screen for mutation by heteroduplex/SSCP analysis, followed by sequence of *P57^{KIP2}* exons)

GENETIC COUNSELING

1. Recurrence risks
 - a. Probably a low recurrence risk in cases of negative family history, normal karyotype, and absence of identifiable molecular etiology
 - b. Up to 50% of recurrence risk in cases of positive family history and normal karyotype
 - c. Up to 50% recurrence risk in cytogenetically detected maternal 11p15 translocation or inversion
 - d. An undetermined recurrence risk in cytogenetically detected paternal 11p15 duplication
 - e. A very low recurrence risk in cases of paternal 11p15 uniparental disomy as this event arises from a postzygotic somatic recombination
 - f. Up to 50% recurrence risk if a *P57^{KIP2}* mutation is present in a parent (usually maternally transmitted)
2. Prenatal diagnosis
 - a. Maternal serum alpha fetoprotein screening: may be elevated in a fetus with omphalocele
 - b. Prenatal Ultrasonography
 - i. Fetal overgrowth (macrosomia)
 - ii. Polyhydramnios
 - iii. Enlarged placenta
 - iv. A long umbilical cord
 - v. Macroglossia
 - vi. Distended abdomen
 - vii. Abdominal wall defects
 - viii. Organomegaly
 - ix. Renal anomalies
 - x. Cardiac anomalies
 - c. Cytogenetic studies
 - i. Possible if a cytogenetic abnormality has been identified in the proband and one parent
 - ii. To identify translocations, inversions, and duplications involving 11p15
 - d. Molecular analysis
 - i. Uniparental disomy
 - ii. Mutation analysis of *P57^{KIP2}* provided the mutation is documented in the previously affected child

DIAGNOSTIC INVESTIGATIONS

1. Transitory neonatal hypoglycemia (spontaneous regression during the first 4 months of life) (63%)
2. Neonatal polycythemia (20%)
3. Hypercholesterolemia, hyperlipidemia, hypothyroidism, thyroxine-binding globulin deficiency: rare occurrence
4. Periodic abdominal ultrasonography for organomegaly and embryonal tumors, followed by MRI or CT if indicated
5. Radiography
 - a. Advanced bone age
 - b. Chest radiography to rule out rare neural crest tumors such as thoracic neuroblastoma

3. Management
 - a. Early detection and close monitoring for hypoglycemia to reduce the risk of central nervous system complications
 - b. Partial tongue resection for cosmetic purpose and to relieve severe airway obstruction
 - c. Surgical risks related to hypoglycemia or difficulty in intubation secondary to macroglossia
 - d. Management of abdominal wall defects, gastrointestinal malformations, and renal anomalies
 - e. Orthopedic follow-up of hemihyperplasia
 - f. Management of structural renal abnormalities
 - g. Management of embryonal neoplasms

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Fig. 1. Five infants with BWS showing hemangioma, macroglossia and umbilical hernia.





Fig. 2. An infant with BWS showing macroglossia, ear crease, and umbilical hernia.



Fig. 5. A young adult with BWS showing macroglossia and post-surgical status of umbilical and inguinal hernia repairs.



Fig. 3. An infant with BWS and a large omphalocele requiring surgical intervention.



Fig. 4. An infant with BWS prior to partial glossectomy.

Behcet Disease

In 1937, Behçet first described three patients with oral and genital ulceration and hypopyon. It is most common in the Middle and Far East with a prevalence of 7 to 8 per 100,000 people, whereas in the United States the prevalence is estimated at 4 per 1,000,000 people.

GENETICS/BASIC DEFECTS

1. A complex multisystem inflammatory disease of unknown cause
2. Considered a relapsing and remitting vasculitis of the small- to medium-sized vessels with following protean manifestations
 - a. Aphthous stomatitis
 - b. Genital ulceration
 - c. Uveitis
 - d. Synovitis
 - e. Gastrointestinal lesions
 - f. Cutaneous lesions
 - g. Central nervous system lesions
 - h. Cardiac lesions
 - i. Vessel lesions
3. Immunopathogenic aspects of Behcet disease
 - a. Neutrophil activation
 - b. Cellular and humoral immunity
 - c. Antigenic stimuli
 - i. Herpes simplex virus
 - ii. Streptococci and superantigens
 - iii. Heat shock proteins (65 kDa, $\alpha\beta$ -crystallin)
 - d. Genetic predisposition to HLA-B51 and antigen presentation
 - e. Retinal-S antigen and HLA-B51 as autoantigens
 - f. Vascular disease and antiendothelial cell antibodies
 - g. Severity and sex: more severe in men
- vi. Herpetiform aphthous ulcers: numerous lesions grouped as small ulcers
- b. Genital ulcers
 - i. Women: located on the vulva, vagina, cervix uteri
 - ii. Men: located on the prepuce and scrotum
 - iii. Lesions resembling the oral aphthae but tend to be deeper and leaving scars
 - iv. Differential diagnosis from other genital ulcers (herpes simplex, syphilis, tropical ulcers, and skin infestations)
- c. Ocular lesions (70–85%)
 - i. Generally follow the genital and oral ulceration by a few years
 - ii. Characterized by severe vasculitis with arterial and venous occlusions
 - iii. Hypopyon (presence of leukocytes in the anterior chamber of the eye)
 - iv. Uveitis
 - v. Hemorrhagic and exudative retinal lesions (retinitis)
 - vi. Marked vitritis
 - vii. Choroiditis
 - viii. Bilateral nongranulomatous inflammation of the iris and ciliary body
 - ix. Intermittent blurring of vision and loss of vision
- d. Skin lesions
 - i. Pustular vasculitic cutaneous lesions: may evolve as lesions of small vessel necrotizing vasculitis from a neutrophilic vascular reaction to a lymphocytic perivascular reaction
 - ii. Erythema nodosum-like lesions: usually occurring on the lower extremities but can be seen on the arms, neck, and face
 - iii. Pseudofolliculitis
 - iv. Papulopustular lesions: neutrophil-induced, vessel-based reaction
 - v. Acneiform nodules

CLINICAL FEATURES

1. Highly variable clinical course with recurrences and remissions
2. Recurrent attacks of oral, genital, ocular, and skin lesions
 - a. Oral aphthous ulcers
 - i. Keystones to diagnosis of Behcet disease according to the classification criteria
 - ii. Often an initial presenting sign
 - iii. Occurring on the buccal mucosa, tongue, gingiva and the soft palate area
 - iv. Minor aphthous ulcers: superficial with a diameter of 2–6 mm, appearing as multiple lesions, and developing within 1–2 days. They heal without scarring within 7–10 days and recur at various frequencies
 - v. Major aphthous ulcers: deeper and painful lesions leaving scars after healing
3. Articular manifestations
 - a. Recurrent seronegative arthritis
 - i. Common findings
 - ii. A nonspecific synovitis
 - b. Monoarthritis
 - c. Polyarthritis
4. Gastrointestinal manifestations
 - a. Ulcerative lesions most frequently occurring in the terminal ileum, caecum, stomach, and intestine
 - b. Symptoms
 - i. Abdominal pain
 - ii. Diarrhea
 - iii. Melena
 - iv. Perforation
5. CNS manifestations (about 1% of patients)
 - a. Headaches
 - b. Meningitis

- c. Meningoencephalitis
- d. Cranial nerve palsies
- e. Peripheral nerve involvement with vasculitis
- f. Cerebellar ataxia
- g. Hemiplegia
- h. Benign intracranial hypertension
- i. Neurologic deficits
- j. Cerebral aneurysm
- k. Cerebral vasculitis and ischaemic stroke: unusual
- l. Personality changes and depression
- m. Dementia
- n. Hearing and vestibular disturbances
- 6. Pulmonary manifestations
 - a. Tracheobronchial ulcerations
 - b. Pleurisy
 - c. Embolism
 - d. Pulmonary arterial aneurysms
 - e. Pneumonitis
 - f. Fibrosis
- 7. Renal involvement: rare
 - a. Glomerulonephritis
 - b. Systemic amyloidosis
- 8. Cardiac manifestations
 - a. Intracardiac thrombosis
 - b. Myocardial infarction
 - c. Pericarditis
 - d. Endocarditis
- 9. Vascular manifestations
 - a. Superficial thrombophlebitis
 - b. Deep thrombophlebitis
 - c. Small vessel vasculitis
 - d. Aneurysm
- 10. Criteria for clinical diagnosis of Behcet disease, proposed by O'Duffy and Goldstein in 1976, require the presence of recurrent oral or genital aphtha along with two additional systemic findings for diagnosis and only one for the diagnosis of the incomplete form
 - a. Criteria
 - i. Aphthous stomatitis
 - ii. Aphthous genital ulceration
 - iii. Uveitis
 - iv. Cutaneous "pustular" vasculitis
 - v. Synovitis
 - vi. Meningoencephalitis
 - b. Diagnosis: at least three criteria present, one being recurrent aphthous ulceration
 - c. Incomplete form: two criteria present, one being recurrent aphthous ulceration
 - d. Exclusion
 - i. Inflammatory bowel disease
 - ii. Systemic lupus erythematosus
 - iii. Reiter's disease
 - iv. Herpetic infections
- 11. The International Study Group criteria were published in 1990 to include positive Pathergy test as one of the criteria to establish the diagnosis of Behcet disease:
 - a. Recurrent oral ulceration: minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in one 12-month period
 - b. Plus 2 of the following criteria (findings applicable only in absence of other clinical explanations)
 - i. Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient
 - ii. Eye lesions: anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist
 - iii. Skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by physician in post-adolescent patients not receiving corticosteroid treatment
 - iv. Pathergy test (a nonspecific pustule that is an inflammatory reaction to needle pricks in approximately 40% of patients, especially during the exacerbation period): Pathergy test is positive when pricking a sterile needle into the patient's forearm results in an aseptic erythematous nodule or pustule that is more than 2 mm in diameter at 24–48 hours

DIAGNOSTIC INVESTIGATIONS

1. Positive skin pathergy
2. Laboratory findings
 - a. Acute-phase response
 - i. Raised erythrocyte sedimentation rate
 - ii. Increased serum levels of C-reactive protein
 - iii. Elevated plasma complement components, such as C3, C4, C9, and factor B
 - b. Disease exacerbations
 - i. Elevated IgG, IgA, IgM
 - ii. Elevated C-reactive protein
 - iii. Elevated α_2 -globulin
 - c. Interleukin (IL)-8 as a serological marker
3. HLA typing
4. Fluorescein angiography, color Doppler imaging and fundoscopic examination to detect retinal features
5. MRI and CT scan to detect the neurologic lesions
6. Histopathological features
 - a. Pathergy lesions
 - i. Leucocytoclastic vasculitis
 - ii. Neutrophilic vascular reaction
 - iii. Polymorphonuclear leucocyte infiltration
 - b. Erythema nodosum-like lesions
 - i. Neutrophilic vascular reaction or vasculitis in the dermis and subcutaneous tissue
 - ii. Perivascular lymphocytic dermal inflammation
 - c. Common histopathological lesions in all organ systems
 - i. Vasculitis
 - ii. Thrombosis
 - iii. Perivascular infiltrates of lymphomononuclear cells
 - iv. Neutrophilic vascular reaction
 - d. Early cutaneous lesions: neutrophilic vascular reaction or leucocytoclastic vasculitis
 - e. Late cutaneous lesions: lymphocytic perivasculitis

GENETIC COUNSELING

1. Recurrence risk
 - a. Patient's sib: not increased

- b. Patient's offspring: not increased
2. Prenatal diagnosis: no prenatal diagnosis reported
3. Management:
 - a. Mucocutaneous lesions
 - i. Topical corticosteroids: useful for oral and genital ulcers
 - ii. Colchicine: beneficial effects on the mucocutaneous symptoms, presumably by inhibiting neutrophil function
 - iii. Treatment with thalidomide: effective for oral and genital ulcers and pseudofolliculitis
 - iv. Systemic corticosteroids: prescribed for erythema nodosum that is refractory to treatment with colchicine
 - b. Ocular lesions
 - i. About 25% of patients eventually develop blindness despite therapeutic intervention
 - ii. Topical mydriatic agents and corticosteroid drops: given for attacks of anterior uveitis
 - iii. Colchicine: prescribed to prevent both anterior and posterior uveitis because of its high degree of efficacy and relatively low toxicity
 - iv. Topical injection of corticosteroids, with systemic administration in some cases: used for acute attacks of posterior uveitis
 - v. Cytotoxic agents (azathioprine, chlorambucil, and cyclophosphamide): help prevent ocular attacks in approximately 50–75% of patients
 - vi. Cyclosporine: beneficial in 70–80% of patients with ocular lesions that have been refractory to the conventional therapies
 - vii. Subcutaneous human recombinant interferon alpha: an effective and fairly well tolerated therapy for Behcet disease
 - viii. Results from therapies: improved vision and decreased pain, saving the individual a potential enucleation
 - c. Arthritis
 - i. Nonsteroidal anti-inflammatory drugs and colchicine: effective for most cases of arthritis
 - ii. Low dose corticosteroids and azathioprine: used in patients whose arthritis is resistant to treatment with nonsteroidal anti-inflammatory drugs, colchicine, or Sulfasalazine
 - iii. Interferon alfa: also highly effective
 - d. Gastrointestinal lesions
 - i. Sulfasalazine and corticosteroids: the principal drugs
 - ii. Bowel rest: obligatory in patients with an acute abdomen and bleeding
 - iii. Surgery: considered for patients with bowel perforation and persistent bleeding
 - e. CNS lesions
 - i. High doses of corticosteroids
 - ii. Supplemented with cytotoxic agents
 - f. Large-vessel lesions
 - i. Treated with a combination of corticosteroids and cytotoxic agents
 - ii. Anticoagulants and antiplatelet agents: used for deep venous thrombosis
 - iii. Surgery for refractory large-vessel disease

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Fig. 1. Aphthae on the tongue, buccal mucosa, and gums of a child with Behcet disease.



Fig. 2. A female patient with Behcet disease showing generalized scars from blisters on the buccal mucosa, trunk, arms, legs, and palms.



Fig. 3. A large aphthous ulcer on mucosal membrane of the lower lip of a patient with acute exacerbation of Behcet disease.

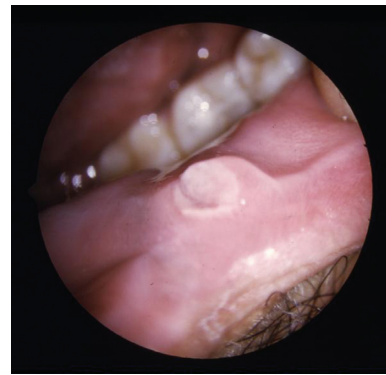


Fig. 4. Occluded retinal vessels and retinal hemorrhage with arterial and venous occlusive vasculitis in a patient with Behcet disease.



Bladder Exstrophy

Bladder exstrophy is a rare developmental anomaly occurring as an isolated defect in about 1/25,000–1/40,000 births.

GENETICS/BASIC DEFECTS

1. Genetics: usually an isolated defect
2. Basic defects
 - a. Probably failure of fusion of the secondary mesoderm (from the primitive streak) in the midline of the anterior abdominal wall, with subsequent rupture of the thin wall consisting only of ectoderm and endoderm
 - b. Early rupture (5th week) resulting in exstrophy of the cloaca, later rupture (7th week) resulting in exstrophy of the bladder

CLINICAL FEATURES

1. Classical bladder exstrophy
 - a. Diagnosis easily made at birth
 - b. Occupy 60% of the patients with the exstrophy-epispadias complex
 - c. Bladder plate protruding just beneath the umbilical cord
 - d. Posterior bladder wall is exposed through a midline abdominal wall defect
 - e. Inferiorly displaced umbilicus located close to the superior margin of the exstrophic bladder
 - f. Rectus muscles divergent on either side of the bladder
 - i. Leading to the separated pubic bones
 - ii. Separation of the pubic bones caused by an outward rotation of the innominate bones and eversion of the pubic rami
 - g. Male patients
 - i. A short epispadiac phallus with a dorsal urethral plate
 - a) Caused by separation of the pubic bones
 - b) Possibly caused by a true deficiency of corporeal tissue
 - ii. A splayed glans
 - iii. Dorsal chordee
 - h. Female patients
 - i. Genital defect analogous to the male but more easily reconstructed
 - ii. Separated mons pubis (both hemiclitoris and labia) (split clitoris and exstrophic vagina)
 - iii. Predisposing to uterine prolapse, especially after pregnancy and delivery, secondary to pelvic floor defect
 - i. Urinary tract abnormalities
 - i. Generally normal upper urinary tract
 - ii. Occasional abnormalities
 - a) Unilateral renal agenesis
 - b) Horseshoe kidney
 - c) Hydronephrosis
 - d) Other renal anomalies
- j. Internal genitalia: usually normal
- k. Fertility and childbearing
 - i. Documented in both sexes but less common in the males
 - ii. C-section advised to avoid injury to continence mechanism
 - iii. Postpartum uterine prolapse common because of aggravation of preexisting abnormal pelvic support
- l. Inguinal hernias
 - i. Incidence: very common
 - a) 56–82% in boys
 - b) 11–15% in girls
 - ii. Incidence of bowel incarceration below one year of age: 10–53%
 - iii. Causes
 - a) Large internal and external inguinal rings
 - b) Lack of obliquity of the inguinal canal
- m. Anus
 - i. Anteriorly placed
 - ii. Fecal continence adversely affected by the divergence of the pelvic musculature
- n. Rectal prolapse
 - i. Virtually always disappears after bladder closure or cystectomy
 - ii. Represents an indication for surgical management of the exstrophied bladder
- o. Spinal abnormalities (6.7%)
 - i. Myelomeningocele
 - ii. Lipomeningocele
 - iii. Scimitar sacrum
 - iv. Posterior laminal defects
 - v. Vertebral fusion
 - vi. Hemivertebrae
- p. Malignancies
 - i. Rare late complication of bladder exstrophy, especially in untreated patients whose bladders are left exstrophic for many years
 - ii. Types of malignancies
 - a) Adenocarcinoma: the most common type, arising from the precursor cystitis glandularis, a consequence of chronic irritation and inflammation of exposed bladder mucosa
 - b) Squamous cell carcinoma and rhabdomyosarcoma
 - c) Adenocarcinoma developing adjacent to the ureterointestinal anastomoses in patients with urinary diversions that mix the urinary and fecal streams
 - d) The risk of developing colon adenocarcinoma is increased 7000-fold after uretero-sigmoidostomy among patients younger than 25 years of age than the general population

- q. Behavioral, social and school competency problems observed in 70% of adolescents and 33% of school aged children
- r. 70% of parents express concern about the children's sexual function or sexual disfigurement
- s. Consider all patients with exstrophy-epispadias complex to be latex-sensitive
- 2. Variants of exstrophy
 - a. Pseudo-exstrophy (exstrophic abdominal wall defect without bladder exstrophy)
 - b. Duplicate exstrophy
 - c. Superior vesical fistula and fissure
 - d. Covered exstrophy and visceral sequestration
- iii. Reduction in the urinary tract infections
- iv. Creation of functionally and cosmetically acceptable external genitalia
- c. Initial bladder closure
 - i. Closure of the pelvic ring
 - a) Important for the initial closure
 - b) Important for the eventual attainment of urinary continence
 - ii. Pelvic osteotomy
 - a) Two main approaches: posterior iliac osteotomy and the anterior innominate osteotomy
 - b) Reduce the tension on the suture lines to help securing the bladder closure
 - c) To restore the pelvic anatomy and thus increase the chances of eventual continence and reduce the likelihood of uterine prolapse
- d. Epispadias repair
 - i. Usually performed at 2–3 years of age before the continence procedure
 - ii. Contributing significantly to the development of bladder capacity
 - iii. Goals
 - a) Reconstruction of the urethra and glans penis
 - b) Encourage the potential of penile length
 - c) Correction of the dorsal chordee
 - d) Achieving adequate skin coverage
 - iv. Penis is generally reconstructible to cosmetically and functionally acceptable form, despite a short phallus
- e. Bladder neck reconstruction
 - i. Usually performed at age of 4–5 years (when toilet training is possible)
 - ii. Require anti-reflux procedure since all exstrophy patients have vesicoureteral reflux
 - iii. Complete urinary drainage achieved with ureteral stents and suprapubic cystostomy tubes
- f. Ureteral reimplantation
- g. Bladder augmentation and continent diversion for patients who have failed bladder neck reconstruction and have an inadequate bladder capacity
- h. Alternatives for exstrophy reconstruction
 - i. For patients with very small bladder plates or hydronephrosis
 - ii. Ureterosigmoidostomies
 - a) Allow children to achieve continence
 - b) Protect upper urinary tracts
 - c) Potential complications: recurrent acute and chronic pyelonephritis, urolithiasis, hyperchloremic hypokalemic metabolic acidosis, ureteral obstruction and the late development of colonic malignancy
 - i. Repair of inguinal hernias at the time of primary closure of bladder exstrophy

DIAGNOSTIC INVESTIGATIONS

1. General assessment
2. Cardiopulmonary assessment
3. Renal ultrasound for baseline examination of the kidneys since increased bladder pressure after bladder closure can lead to hydronephrosis and upper urinary tract deterioration
4. Voiding cystourethrogram
 - a. To rule out bilateral vesicoureteral reflux which is present in nearly all patients with classic bladder exstrophy
 - b. Performed in early childhood to assess bladder capacity in preparation for continence reconstruction

GENETIC COUNSELING

1. Recurrence risk
 - a. Patient's sib: the risk of recurrence of exstrophy or epispadias in a given family is one of 275 births
 - b. Patient's offspring: the risk of a parent with exstrophy producing a child with exstrophy or epispadias is up to one of 70 or 500 times the risk of the general population
2. Prenatal diagnosis possible by ultrasonography
 - a. Absence of bladder filling in the presence of normal kidneys (bladder never demonstrated on the ultrasound) (71%)
 - b. A protuberance on the lower abdomen representing the exstrophied bladder (47%)
 - c. A diminutive penis with anteriorly displaced scrotum (57% of the males)
 - d. A low-set umbilical insertion (29%)
 - e. Abnormal widening of the iliac crests (18%)
 - f. Separation of the pubic rami
 - g. Difficulty in ascertaining the sex of the fetus
3. Management
 - a. Supportive management
 - i. Ligate umbilical cord with suture to avoid bladder mucosal damage by an umbilical clamp
 - ii. Protect bladder
 - a) With clear plastic wrap
 - b) Irrigate the bladder surface with sterile saline each time diaper is changed and the wrap replaced
 - iii. Initiate prophylactic antibiotics
 - b. Goals of the reconstruction of bladder exstrophy
 - i. Preservation of the kidney function
 - ii. Creation of urinary continence

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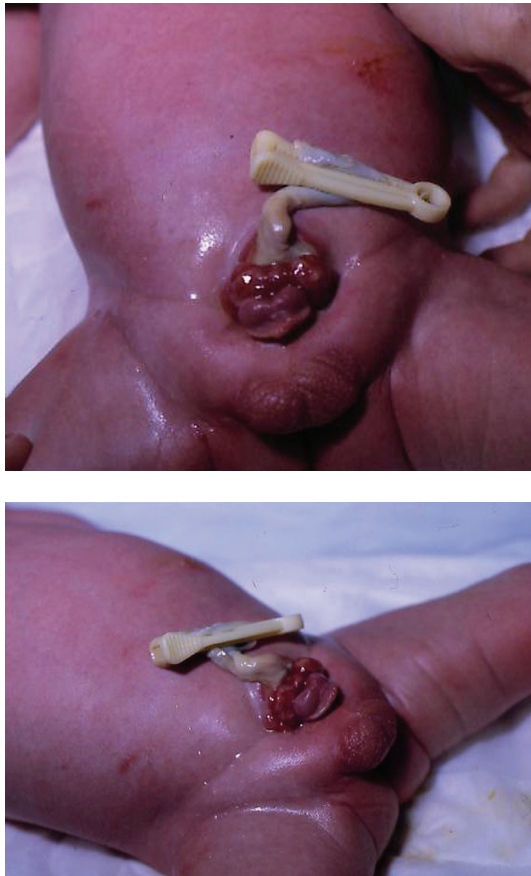


Fig. 1. A newborn male with classic bladder exstrophy showing low insertion of the umbilical cord, a bulging mass of exstrophic bladder, and grossly abnormal external genitalia.

Body Stalk Anomaly

Body stalk anomaly, sometimes also called limb body wall complex, is a rare abdominal wall defect due to failure of the development of the body stalk. Prevalence is estimated to be 0.32 per 10,000 births.

GENETICS/BASIC DEFECTS

1. Sporadic occurrence in most cases, although concordance in twins has been reported
2. Failure in body folding in cranial, caudal and lateral axes during the embryonic stage of development
 - a. Abnormalities of cranial folding leading to pentalogy of Cantrell consisting of the following:
 - i. Cardiac abnormalities
 - ii. Sternal cleft
 - iii. Upper abdominal defect
 - iv. Anterior diaphragmatic hernia
 - v. Deficiency of the diaphragmatic pericardium
 - b. Abnormalities of caudal folding leading to the following:
 - i. Cloacal exstrophy
 - ii. Hypogastric omphalocele
 - iii. Imperforate anus
 - iv. Partial colonic agenesis
 - v. Agenesis of one umbilical artery
 - c. Abnormalities of lateral folding leading to midline omphalocele
 - d. Abnormalities of folding along all three axes resulting in a body stalk anomaly
 - i. Failure to obliterate the extraembryonic cavity that continues to communicate with the intraembryonic cavity
 - ii. Creation of a large ventral wall defect that is covered by an amnioperitoneal membrane which contains the abdominal viscera and inserts directly into the chorionic plate
 - iii. The fetus appearing to be directly attached to the placenta as the umbilical cord is significantly shortened or absent
 - iv. Frequent kyphoscoliosis owing to limited truncal flexion
3. Possible causes of the anomaly
 - a. Early amnion rupture before obliteration of the extraembryonic coelom
 - b. Abnormal splitting of the embryo at the fourth gestational week
 - c. Disturbance of the blood flow due to vascular rupture, as described in cocaine users
 - d. A special situation in monozygotic twins
 - e. Maternal uniparental disomy of chromosome 16 in a fetus with body stalk anomaly suggesting placental insufficiency or imprinting effects as cause of this anomaly

4. Pathogenesis
 - a. The umbilical cord, derived from a small mass of mesoderm (body stalk), attaches the embryo to the wall of the blastocysts
 - b. Abnormal development of the body stalk resulting in an absent or rudimentary umbilical cord
 - c. Consequences
 - i. Direct attachment of fetus to the placenta
 - ii. Abdominal viscera lying in a sac outside the abdominal cavity covered by amnion

CLINICAL FEATURES

1. A large anterior abdominal wall defect with a large omphalocele
 - a. Outside the abdominal cavity containing thoracic and/or abdominal organs
 - b. Covered by amnion
 - c. Appears continuous with (adherent to) the placental membranes
2. Absent, rudimentary, or extremely short umbilical cord. A severe type of short umbilical cord syndrome may be a variant of the body stalk anomaly
3. Two-vessel cord
4. Severe kyphoscoliosis
5. Placenta directly attached to the amnioperitoneal sac
6. Extensive associated anomalies
 - a. Hypoplasia of the lungs
 - b. Anal atresia (imperforate anus)
 - c. Agenesis of the colon
 - d. Intestinal atresia
 - e. Exstrophy of the cloaca
 - f. Vaginal atresia
 - g. Agenesis of uterus and gonads
 - h. Absence of external genitalia
 - i. Hypoplastic kidneys
 - j. Absence of diaphragm
 - k. Diaphragmatic hernia
 - l. Spina bifida
 - m. Dysplastic thorax
 - n. Occasional coexistence of the syndrome with limb malformations (mostly lower extremities) and amniotic bands
7. Fetal death caused by abruptio placentae
8. Liveborn infant die shortly afterward

DIAGNOSTIC INVESTIGATIONS

1. Radiography to document skeletal anomalies
2. Cytogenetic analysis
 - a. No specific anomaly
 - b. Placental karyotyping: report of a case with placental trisomy 16 and maternal uniparental disomy (UPD)

GENETIC COUNSELING

1. Recurrence risk
 - a. Patient's sib: not increased
 - b. Patient's offspring: not surviving to reproductive age
2. Prenatal diagnosis
 - a. High maternal serum alpha fetoprotein
 - b. Ultrasonography
 - i. Can be diagnosed as early as the first trimester by transvaginal sonography
 - ii. A large abdominal anterior wall defect with abdominal organs in a sac outside the abdominal cavity in apparent continuity with (adherent to) the placental membranes
 - iii. An extremely short or absent umbilical cord
 - iv. Severe kyphoscoliosis
 - v. Polyhydramnios
 - vi. Oligohydramnios
 - vii. Two vessel cord
 - viii. Sonographic signs alone expect an unequivocal poor prognosis
 - c. Amniocentesis
 - i. Elevated amniotic fluid alpha fetoprotein level
 - ii. Abnormal acetylcholinesterase
 - iii. Normal chromosomes
3. Management: newborn with the body stalk anomaly, uniformly fatal

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Fig. 1. An extremely premature neonate with body stalk anomaly. Short umbilical cord (7.5 cm with 5 cm fused with placenta) and a large amnioperitoneal sac between the abdomen and the placenta are evident. The sac was filled with internal viscera. In addition, there were anal and urethral atresia, rectovesical fistula, left renal agenesis, lumbosacral meningocele, severe scoliosis, and lumbosacral hypoplasia.



Fig. 2. An infant with body stalk anomaly showing Potter facies, severe kyphoscoliosis, and a large amnioperitoneal sac outside the body. The sac contained abdominal organs. The umbilical cord was absent. Limb and vertebral defects illustrated in the radiographs.



Fig. 3. Another infant with body stalk anomaly showing anterior abdominal wall defect with a large sac containing abdominal organs, exstrophy of the bladder, and clubfeet.

Branchial Cleft Anomalies

Abnormal persistence of branchial apparatus remnants results in branchial anomalies.

GENETICS/BASIC DEFECTS

1. Embryology of the fetal branchial apparatus
 - a. A derivative of a foregut, developed during the second fetal week
 - b. Consisting of five paired pharyngeal arches, separated internally by four endodermal pouches and externally by four ectodermal clefts
2. Embryology of the branchial clefts
 - a. First branchial cleft
 - i. Giving rise to the Eustachian tube, tympanic cavity, and mastoid antrum
 - ii. Contributing to the formation of the tympanic membrane
 - iii. The only cleft to contribute to the adult structure is the external auditory canal.
 - b. Second, third, and fourth branchial clefts
 - i. Known as the cervical sinus of His (part of an ectodermally lined depression)
 - ii. Obliteration of the cervical sinus as the second and fifth branchial clefts merge
 - c. Second branchial pouch
 - i. Lined by ectoderm
 - ii. Contributing to the palatine tonsil and tonsillar fossa
 - d. Third branchial pouch: forming the following structures
 - i. Inferior parathyroid gland
 - ii. Thymus
 - iii. Pyriform sinus
 - e. Fourth branchial pouch: forming the following structures
 - i. Superior parathyroid gland
 - ii. Apex of the pyriform sinus
3. Pathogenesis of branchial cleft anomalies: remains controversial
 - a. Arising from incomplete obliteration of the cervical sinus of His
 - b. Arising from buried epithelial cell rests
4. Genetics: autosomal dominant inheritance in some families

CLINICAL FEATURES (KOELLER, 1999)

1. Manifestation of branchial cleft anomalies
 - a. Cyst
 - i. An epithelial-lined structure without an external opening
 - ii. Most common branchial cleft anomalies (75%)

- b. Sinus
 - i. A blind tract with an opening externally through the skin on the side of the neck representing persistence of a branchial groove
 - ii. A blind tract with an opening internally into the foregut representing persistence of a branchial pouch
 - c. Fistula
 - i. A tract communicating between the skin externally (a patent abnormal canal opening externally on the neck surface) and the foregut internally (within the pharyngeal mucosa)
 - ii. Representing persistence of a branchial groove with its corresponding pouch and without branchial membrane between them
 - d. Skin tag: a branchial remnant presenting in the lateral neck
 - e. Bilateral branchial cleft anomalies
 - i. Occurring in 2–3% of cases
 - ii. Often familial
2. First branchial cleft cyst
 - a. Accounting for only 5–8% of all branchial cleft defects
 - b. Most commonly seen in middle-aged women
 - c. Usually manifesting as recurrent abscesses or other inflammation (sinus tract) either around the ear or at the angle of the mandible
 - d. History of recurrent parotid abscesses unresponsive to antibiotics and drainage
 - e. Cystic drainage into the external auditory canal
 - i. Aural fistulas
 - ii. Auricular swelling
 - iii. Otitis
 - iv. Otorrhea
 - v. A cervical skin tag at birth
 - f. Occasional sinus tract extending to the hyoid bone
 - g. Cyst related to the parotid gland
 - i. Forming abscess and produce parotitis
 - ii. May be associated with facial nerve palsy
 3. Second branchial cleft cyst
 - a. Most common developmental anomalies arising from the branchial apparatus
 - b. Cysts
 - i. Accounting for at least three-fourths of branchial cleft anomalies
 - ii. Typically occurring between 10 and 40 years of age
 - c. Location of the cysts
 - i. Most commonly in the submandibular space
 - ii. Anywhere along a line from the oropharyngeal tonsillar fossa to the supraclavicular region of the neck
 - d. Signs and symptoms of second branchial cleft cyst
 - i. Usually appearing as painless, fluctuant masses in the lateral portion of the neck adjacent to the

- anteromedial border of the sternocleidomastoid muscle at the mandibular angle
 - ii. Enlarge slowly over time
 - iii. Painful and tender if secondarily infected
 - iv. Highly suggestive in a young patient with a history of recurrent inflammation in the region of the mandibular angle
 - v. Ostium usually noted at birth just above the clavicle in the anterior neck if a fistula is present
- e. Fistulas and sinuses
 - i. Almost always present at birth
 - ii. With a small pinpoint external opening
 - iii. May go unnoticed for years if there is no drainage
 - iv. Symptoms consisting of continuous or intermittent mucoid drainage and recurrent attacks of inflammation that often follow mild trauma or an infection of the upper respiratory tract
 - v. Occasional formation of cellulitis and abscess
 - vi. Probing of the track producing irritation of the vagus nerve
 - vii. Usually unilateral
 - viii. Found in several members of the same family
- 4. Third branchial cleft cyst
 - a. Extremely rare
 - b. Most cysts located in the posterior cervical space posterior to the sternocleidomastoid muscle
 - c. Constituting the second most common congenital lesion of the posterior cervical space of the neck after cystic hygroma
 - d. Usually manifesting as a painless, fluctuant mass in the posterior triangle area of the neck
 - e. Mass usually distending during a viral infection of the upper respiratory tract
- 5. Fourth branchial cleft cyst
 - a. Extremely rare
 - b. Usually manifesting as a sinus tract rather than a cyst or fistula
 - c. Majority of the lesions occurring on the left side
- c. Third branchial cleft cyst
 - i. Most commonly appearing as a unilocular cystic mass centered in the posterior cervical space
 - ii. Cyst fluid varying in signal intensity on T1-weighted images depending on the protein concentration and is typically hyperintense relative to muscle on T2-weighted images
- d. Fourth branchial cleft cysts
 - i. Connected with the pyriform sinus
 - ii. Appearing similar to an external or mixed laryngocele
- 2. Ultrasonography
 - a. A fluctuant, compressible, anechoic or hypoechoic mass
 - b. May have fine internal debris
- 3. Sinogram or fistulogram with radiopaque dye
 - a. To help confirming the diagnosis
 - b. To identify length and location of the fistulous tract
 - c. To identify an associated cyst

GENETIC COUNSELING

1. Recurrence risk
 - a. Patient's sib
 - i. Not increased in *de novo* case
 - ii. 50% recurrence risk if a parent is affected with an autosomal dominant disorder
 - b. Patient's offspring: 50% in autosomal dominant inheritance
2. Prenatal diagnosis by ultrasonography possible by demonstrating a cystic neck mass in the fetus with differential diagnosis including hemangioma, dermoid cyst, neuroblastoma, congenital cystic hygroma, teratoma, epignathus, esophageal duplication, goiter, and laryngocele
3. Management
 - a. First branchial cleft cyst: complete surgical excision (only curative therapy)
 - b. Second and third branchial cleft cysts: surgical excision recommended because of increased frequency of secondary infection
 - c. Recurrence risk uncommon after surgical excision
 - d. Antibiotics required for treating infections or abscess

DIAGNOSTIC INVESTIGATIONS

1. CT scans/MRI imagings
 - a. First branchial cleft cyst
 - i. Appearing as a cystic mass either within, superficial to, or deep to the parotid gland
 - ii. Variable wall thickness and enhancement: increase with recurrent infections
 - iii. Difficult to differentiate from other cystic mass of the parotid gland
 - b. Second branchial cleft cyst
 - i. Typically well-circumscribed, homogeneously hypoattenuated masses surrounded by a uniformly thin wall
 - ii. Increased mural thickness after infection
 - iii. "Beaked sign" (a curved rim of tissue or "beak" pointing medially between the internal and external carotid arteries) considered a pathognomonic imaging feature of a second branchial cleft cyst

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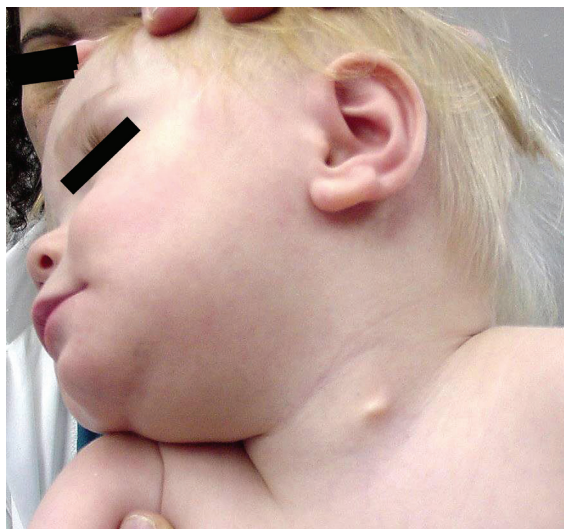


Fig. 1. A branchial cleft cyst in the left side of the neck.

