Potter’s Syndrome

History

In 1946 Edith Louise Potter (b.1901 – d.1993), a pediatric pathologist at the University of Chicago Lying-In Hospital, described anomalies of the fetus due to oligohydramnios. The condition itself has been documented since the late 17th century and was considered to be an extremely rare condition. In one of her more famous manuscripts, Potter analyzed approximately 5000 necropsies performed on fetuses and newborn infants over a period of ten years, and found that 20 infants presented with bilateral renal agenesis (BRA) (1:250). From her studies she was able to deduce the sequence of events that leads to what is now known as Potter Syndrome, Potter Sequence, or Oligohydramnios Sequence. As well as to accurately describe and assign facial characteristics of the affected, which are known as Potter facies.

Since its initial characterization, Potter Syndrome has been defined into five distinct subclassifications. Classic Potter Syndrome occurs when the infant has bilateral renal agenesis. True BRA also presents with bilateral agenesis of the ureters. Potter Syndrome Type I is due to Autosomal Recessive Polycystic Kidney Disease (ARPKD), which occurs at a frequency of approximately one in 40,000 infants and is linked to a mutation in the gene PKHD1. Potter Syndrome Type II is due to Renal Adysplasia (RA), which can also fall under the category known as hereditary renal adysplasia (HRA). Potter Syndrome Type III is due to Autosomal Dominant Polycystic Kidney Disease (ADPKD) linked to mutations in the genes PKD1 and PKD2. Potter Syndrome Type IV occurs when a longstanding obstruction in either the kidney or ureter leads to cystic kidneys. This can be due to chance, environment, or genetics. In all five instances, a lack or reduced volume of fetal urine typically leads to oligohydramnios and results in the physical deformities and prognosis described below.

* This statistic (of one in 250) does not imply that Classic Potter Syndrome occurs in one out of 250 infants. This statistic was obtained from a study published in 1946 of 5000 expired infants that were allowed or obligated to be subjected to a routine or requested autopsy or necropsy.

* In this context, a manuscript is a peer reviewed and formally published article in a scientific journal describing the research methods and obtained results, as well the hypotheses from a study.

Classic Potter’s Syndrome

Classic Potter Syndrome occurs when the developing fetus has bilateral renal agenesis, which also presents with ureteral agenesis (UA). BRA has been estimated to occur at a frequency of approximately 1:5000 infants. However, recent analysis has estimated that the condition may occur at a much greater frequency. The condition has been reported to occur twice as common in males as in females, suggesting that certain genes of the Y chromosome may act as modifiers. However, no candidate genes on the Y chromosome have yet been identified. BRA appears to have a predominantly genetic etiology and many cases represent the most severe manifestation of an autosomal dominant condition with incomplete penetrance and variable expressivity. There are several genetic pathways that could result in this condition. To date, few of these pathways or candidate genes have been considered or analyzed regarding this specific syndrome. The majority of possible pathways are autosomal recessive in nature and do not coincide with the frequency or penetrance at which BRA occurs. Additionally, candidate pathways would be expected to involve genes expressed in the developing urogenital system (UGS). Often, these same genes and/or pathways of interacting genes are expressed in the developing UGS and also expressed in the Central Nervous System (CNS), gut, lung, limbs, and eyes. This often makes it difficult to say with complete certainty that these genes are responsible for a predominantly renal disease.
Normal kidney development

In humans, the metanephros is detectable by the fifth gestational week as two small areas in the mesoderm close to the pelvic aorta. It is approximately at this time that the nephric duct produces a ureteric bud that has, or will soon invade the aggregate of cells known as the metanephric mesenchyme. The ureteric bud is stimulated by genetic signals emanating from the metanephric mesenchyme, and brings with it new genetic signals that will help the kidney form. The ureteric bud will grow into, and branch several times within, the metanephric mesenchyme. Eventually, the ureteric bud will form the collecting ducts and the ureters. The primitive nephric duct will degenerate to some degree, but portions of it will go on to form the correct gender specific organs. The ureteric bud, once it has invaded, stimulates certain cells within the metanephric mesenchyme to condense around the tips of the branches of the ureteric bud within the metanephric mesenchyme, and eventually form nephronic units. In humans, all of the branches of the ureteric bud and the nephronic units have been formed by 32 to 36 weeks of gestation. However, these structures are not yet mature, and will continue to mature after birth. Once matured, humans have been estimated to possess approximately one million nephronic units (approximately 500,000 per kidney). The lower portions of the ureteric bud will migrate downward, and connect with the bladder, forming the ureters. The ureters will carry urine to the bladder for excretion within the amniotic sac. As the fetus develops, the torso elongates and the kidneys migrate upwards, which causes the length of the ureters to increase. The development of the kidney is critical to the development of the fetus by the means of urine production. A large proportion of the amniotic fluid that surrounds the fetus is comprised of fetal urine. The amniotic fluid serves many functions to the developing fetus. It is responsible for cushioning the fetus and preventing the uterus from compromising it, thereby allowing adequate space for the fetus to properly grow. Also, the pressure of the amniotic fluid is critical to the growth, formation and expansion of the alveolar sacs in the developing lungs.

Phenotypes of Classic Potter’s Babies

The failure of the metanephros to develop in cases of BRA and some cases involving unilateral renal agenesis is due primarily to the failure of the nephric duct to produce a ureteric bud capable of inducing the metanephric mesenchyme. The failed induction will thereby cause the subsequent degeneration of the metanephros by apoptosis and other mechanisms. The nephric duct(s) of the agenic kidney(s) will also degenerate and fail to connect with the bladder. Therefore, the means by which the fetus produces urine and transports it to the bladder for excretion into the amniotic sac has been severely compromised (in the cases of URA), or completely eliminated (in the cases of BRA). The decreased volume of amniotic fluid causes the growing fetus to become compressed by the uterus. This compression can cause many physical deformities of the fetus, most common of which is Potter facies. Lower extremity anomalies are frequent in these cases, which often presents with clubbed feet and/or bowing of the legs. Sirenomelia, which occurs approximately in 1:45,000 births (Banerjee A, 2003; Indian J Pediatr) can also present. In fact, nearly all patients reported with sirenomelia have BRA (Siegel MJ, 2000; J Peri), suggesting that sirenomelia is due mainly as a result of BRA or RA. Other anomalies of the Classic Potter Infant include a parrot beak nose, redundant skin, and the most common characteristic of infants with BRA which is a skin fold of tissue extending from the medial canthus across the cheek. The adrenal glands often appear as small oval discs pressed against the posterior (back) abdomen, due to the absence of upward renal pressure. The bladder is often small, nondetectable and may be filled with a minute amount of fluid. In males the vas deferens may be absent, while in females the uterus and upper vagina may be absent. Other abnormalities include anal atresia, absence of the rectum and sigmoid colon, esophageal atresia, and a single umbilical artery. Additionally, the alveolar sacs of the lungs fail to properly develop as a result of the reduced volume of amniotic fluid. Labor is often induced between 22 and 36 weeks of gestation (however, in some cases the pregnancy may go to term) and unaborted infants typically survive for only a few minutes to a few hours. These infants will eventually expire as either a result of pulmonary hypoplasia or renal failure.
To date, Classic Potter Syndrome has proved to be 100% lethal in all cases of singleton births. Various other forms of the syndrome are, or are near, 100% lethal. Additionally, no genetic mutation, disease, condition, or anomaly has been linked to be the cause of Classic Potter Syndrome.

**Definitions of medical terminology**

1. **Oligohydramnios**: Oligo-, few or scanty. An insufficient volume of amniotic fluid.
2. **Necropsy**: A postmortem examination or autopsy.
3. **Bilateral**: Bi-, two. –Lateral, side. On, with, or pertaining to two sides. The kidneys are bilateral organs, one on each side of the body. The ureters (See 8), testicles, ovaries, fallopian tubes, lungs and eyes are also bilateral organs. The arms and legs are bilateral structures of the body.
4. **Renal**: Of, or pertaining to, the kidneys.
5. **Agenesis**: A-, without. Genesis; beginning, starting point. Therefore, agenesis refers to the lack of the development of a tissue, organ or organism. In the cases of bilateral renal agenesis, both kidneys are completely absent (missing).
6. **Sequence**: In the terms of this synopsis: this refers to a sequence of events that could begin with any number of factors but arrives at the same conclusion.
7. **Facies**: Of, or pertaining to, physical characteristics or expressions of the face.
8. **Ureters**: Muscular tubes that carry urine from the kidney to the bladder.
9. **Autosomal**: An autosome refers to any chromosome that is not a sex chromosome (which are either chromosome X or chromosome Y). Therefore, autosomal refers to chromosome pairs 1 through 22, as the 23rd chromosomal pair is the sex specific chromosomes.
10. **Autosomal Recessive**: Autosomal Recessive is a genetic term that refers to the means a trait could be inherited and the phenotype (see 32) of the gene. In this instance, both parents are each normal, yet are heterozygous\(^a\) carriers of the abnormal allele\(^b\) and typically do not have any of the physical characteristics of the phenotype. Therefore, there is a 25% chance of having an affected (homozygous\(^c\) recessive) offspring. Because of this low probability and the fact that many families in Western societies now have fewer than four children, it is unusual for more than one child in a family to have an autosomal recessive disease. Sickle cell anemia, cystic fibrosis and phenylketonuria (PKU) are other examples of autosomal recessive diseases.

\(^a\) Heterozygous (**Hetero-, different, or other**) refers to the two forms of the same gene (normal and abnormal). Each person carries two copies of a gene (one from their mother and one from their father). A person that carries one normal form of the gene and one abnormal form of a gene is considered to be a heterozygous carrier (as in only one copy, out of two, of the gene is normal. The phenotype of the heterozygous carrier may be determined by either one, or both of the alleles. However, because the normal form of the gene is dominant (in an autosomal recessive instance), heterozygous carriers of a recessively abnormal gene are typically quite normal.

\(^b\) An allele is one of the several alternative forms of a gene occupying a certain location on a chromosome (locus). As genes may naturally change their sequence due to evolution or other mechanisms, a gene, when naturally occupying its correct location on a chromosome is called an allele.

\(^c\) Homozygous (**Homo-, same or equal**) also refers to the two forms of the same gene. Homozygous in genetic terms means that both the copies of the gene are the same, both are normal, or both are abnormal.
Example of Autosomal Recessive Inheritance

Let’s say that “gene A” is responsible for growing your eyebrow hair. “A” is the normal form of “gene A” and “a” is the abnormal form of “gene A.” The mother and father of the family in the chart are heterozygous carriers for “gene A.” Let’s suppose that as long as a person has one normal form of “gene A” they will be able to grow eyebrows. Additionally, let’s simplify matters by saying that all of the children were conceived at the same time (quadruplets).

<table>
<thead>
<tr>
<th>Mother</th>
<th>Father</th>
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<tr>
<td>Aa</td>
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<th>Children</th>
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<th>3</th>
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<tr>
<td></td>
<td>AA</td>
<td>Aa</td>
<td>aA</td>
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</table>

Child 1 is normal for “gene A,” and is not a carrier of the disease (Absent eyebrow syndrome) as he has received one normal form of “gene A” from mom and one from dad. There is a 25% chance of this happening. Child 1 will have very healthy eyebrows. Child 2 is heterozygous for “gene A.” He received the normal form from mom and the abnormal form from dad. This child will have normal looking eyebrows but is a carrier. Child 3 is also heterozygous for “gene A,” but in this case he received the normal form of the gene from dad and the abnormal form from mom. This child will also have normal eyebrows and is also a carrier. Child 4 is homozygous for “gene A,” having inherited an abnormal form from mom and an abnormal form from dad. There is a 25% chance of this happening, and this child will not have any eyebrows, and, is considered to be affected. The overall statistical picture of these children is, 75% unaffected (having eyebrows) and 25% affected (not having eyebrows). However, in the real world each child individually has a one in four chance of being affected, and a one in two chance of being a heterozygous carrier.

11. Polycystic Kidney: Polycystic Kidney Disease typically refers to a genetic disease that produces many (poly-, many; inferred is “of the same”…many of the same) fluid filled sacks on and in the kidney, which are small and each are very similar in proportion, size and nature. This condition is different from that which is defined as Multicystic Kidney Disease (multi- also means many, but does not infer uniformity). Bilateral Multicystic kidneys can also lead to Potter’s Sequence. While Polycystic kidneys and multicystic kidneys both have numerous cysts, the cysts of the multicystic kidney are not uniform in size, being medium to large in size, and they are fewer in number than the cysts found on a polycystic kidney. Yet, the eventual outcome of the two different diseases can be very similar.

12. Mutation: A change from what was considered or previously considered to be normal. In the broad sense, a mutation is any discontinuous change in the genetic constitution of an organism. In the narrow sense, mutation usually refers to a “point mutation,” which is a change along a very narrow portion of the DNA sequence. Mutations may be dominant or recessive.

13. Renal Adysplasia: Adysplasia refers to a combination of terms originally coined by Bucheta, et al. 1973. Bucheta’s term attempts to combine the terms agenesis (complete lack of formation of a tissue which under normal circumstances should form and develop) with dysplasia (a tissue which has formed to a certain degree, but can not be considered as completely normal, as it possess certain (or many) architectural deformities). The root, -plasia, refers to the proper formation or growth of an organism, structure, or tissue. Dys- can most directly be correlated to the exact opposite of proper, or correct. Therefore, a dysplastic kidney is one that has improperly formed. However, adding the “A” in front of the term “dysplastic” (in regards to kidneys, and other
bilateral organs) implies that one of the kidneys has failed to form while the other kidney is present, but improperly formed.

14. **Autosomal Dominant:** A genetic term that refers to the means a trait could be inherited and the phenotype (see 32) of the gene. An autosomal recessive disease/disorder occurs when an abnormal gene from only one parent is capable of causing disease in the child, even when the normal gene from the other parent is present. Huntington’s Disease is also an example of an autosomal dominant disease, as well as osteogenesis imperfecta and familial hypercholesterolemia.

**Example of Autosomal Dominant Inheritance**

Let’s use “gene B” this time and say that as long as a person has both normal forms of the gene “BB,” their eyebrows won’t fall off when they’re 55 years old. But, if they have one abnormal form of the gene “Bb” or two abnormal forms “bb,” their eyebrows will fall off on their 55th birthday. The mother and father of the family in the chart are affected heterozygous carriers of the gene, but they’re only 30 years old, so they don’t know that they are carriers yet. But, in 25 years, their eyebrows will fall off!

<table>
<thead>
<tr>
<th>Mother</th>
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<tr>
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<tr>
<td>2</td>
<td>Bb</td>
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<td>4</td>
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Child 1 is lucky! He received a normal gene from mom and a normal gene from dad. He will not lose his eyebrows when he turns 55 and is not an affected carrier of the abnormal gene. However, Child 2 and Child 3 are affected heterozygous carriers for the abnormal gene. Their eyebrows will fall out when they turn 55, and each child has a 50% chance of passing the abnormal gene on to their children. Child 4 is definitely affected as he is a homozygous carrier for the abnormal gene. Unfortunately, this child has a 100% chance of passing the abnormal gene on to his children.

15. **Ureteral Agenesis:** Ureteral: of, or pertaining to the ureters. Ureteral agenesis is also seen in cases of BRA. In fact, it has been determined that if a ureter can be found during autopsy, then kidney tissue (no matter how small) will also be found on the end of the ureter where it would otherwise connect with a normal kidney. As of to date, no case of bilateral ureteral agenesis has ever been seen when the kidneys are still present.

16. **Y chromosome:** The sex chromosome whose presence indicates that the individual is a genetic male. A.K.A. the normal male sex determining chromosome.

17. **Modifiers:** Refers to other genes or the protein products from other genes that modify the normal or abnormal gene of interest and its expression or its protein product.

18. **Etiology:** Also spelled Aetiology in areas outside the United States. _Aitia_; cause. _-Logos, discourse_. The science that deals with determining the causes and origins of a disease or disorder.

19. **Penetrance:** The proportion of individuals with a given genotype (see the examples in 10 and 14) that actually show the expected phenotype (see 32). For an autosomal recessive disorder, this proportion is typically 25% (give or take a few percentage points). For an autosomal dominant disorder, this proportion is approximately 100%, but can be reduced by modifier genes.

20. **Expressivity:** Refers to the degree of which a gene is expressed as a phenotype (see 32).

21. **Urogenital System (UGS):** the system of tissues derived from specific cells that are, or will eventually mature to be, the tissues that comprise the kidney, ureter (and its branches), bladder, gonads, and sex specific genitalia.

22. **Central Nervous System (CNS):** A general term that loosely refers to the brain and the spinal cord. It does not include the nerves, neurons (nerve cells), or neuronal (of or pertaining to a neuron) that extend from the brain or spinal cord.
23. Metanephros: Meta-, after, or beyond. Nephr-, of or pertaining to the kidney. Therefore, metanephros refers to the kidney after a time point which normal development of the kidney should have occurred. Otherwise known as the adult or permanent kidney.

24. Mesoderm: Meso-, middle. –Derm, skin, or tissue. One of the three primary germ cell layers in the developing embryo. The other two are the ectoderm and endoderm, the mesoderm development occurs after the ectoderm, but before the endoderm.

25. Pelvic Aorta: A major blood vessel that carries blood from the heart to the pelvic (hip) region.

26. Nephric Duct: A tube like structure of primitive tissue present in the mesoderm, that forms the ureteric bud (see 27). If the ureteric bud successfully invades the metanephric mesenchyme, the lower portions of the nephric duct will form the ureters and connect with the bladder. The upper regions of the nephric duct will go on to form sex specific genitalia.

27. Ureteric Bud: A finger like projection of epithelial tissue extending from the nephric duct.

28. Mesenchyme: Mesenchyme is not a germ layer but a special type of tissue (basically connective tissue) consisting of unspecialized cells. Most mesenchyme is from the mesoderm but it may arise from other germ layers.

29. Nephronic Units: Structures within the kidney that filter impurities from the blood and produce urine.

30. Torso: The chest and abdominal region (trunk of the body).

31. Alveolar Sacs: Located in the lungs, the alveolar sacs will be responsible for the proper respiration (the exchange of atmospheric gases into and out of the blood stream) of the infant once it is born and must breathe air on its own. Also known as alveoli.

32. Phentype: Physical characteristics of an individual due to their genetic makeup. Example: Your eye color is the phenotype of the genes responsible for determining your eye color. Abnormal genes can cause abnormal phenotypes.

33. Unilateral: Uni-, one. –Lateral, side. Of, or pertaining to only one side.

34. Induce: Introducing the new and necessary signals for further development.

35. Apoptosis: Programmed cell death. In the event that a cell does not develop properly, certain signals and pathways within the cell will be activated to destroy it’s self. This is done so that the abnormal cell does not corrupt the entire organism. Cancer is an example of improperly formed cells that do not undergo apoptosis.

36. Amniotic Sac: Also known as “the bag of waters,” it formed by two membranes with in the uterus. The chorion is the outer most membrane, and the amnion is the inner most membrane and contains the amniotic fluid and the fetus.

37. Potter Facies: The facial characteristics of Potter babies which includes: wide set eyes, squashed nose, receding chin, large and low set ears, which presents as if a nylon stocking has been pulled over the infant’s face.

38. Sirenomelia: Mermaid’s syndrome, where the legs of the infant are fused together. Nearly all mermaid babies have BRA.

39. Parrot beak nose: where the nose is thin and the tip of the nose is turned downward.

40. Redundant skin: also called accessory skin, Potter’s babies often appear to have too much skin for their little bodies.

41. Canthus: the corner of the eye closest to the nose.

42. Adrenal glands: Also called suprarenal glands, these small glands form above the kidneys and produce the hormone adrenaline.

43. Upward Renal Pressure: Because the kidney and the adrenal gland above it actually touch each other, they influence the shapes of each others developing structure.

44. Nondistensible: Unable to expand or be filled. As the empty bladder is filled with urine, it is capable expanding, or distending, to accommodate the volume of urine, like a balloon.

45. Vas deferens: Unique to males, the vas deferens is the coiled tube like structure that connects the testis with the urethra. It acts as a duct to convey sperm to the ejaculatory duct and the urethra for ejaculation.

46. Seminal Vesicles: Two small structures located behind the bladder that contribute fluid to the ejaculate.

47. Anal atresia: Anus, the opening of the rectum. Atresia, the absence of a normal opening. In anal atresia, also called imperforate anus, the opening of the anus is fused and therefore solid waste cannot be excreted from the body.
48. **Sigmoid colon**: The lower ‘S-shaped’ colon of the large bowel.
49. **Esophageal**: Of, or pertaining to the esophagus.
50. **Duodenal**: Of, or pertaining to the duodenum, which is the first part of the small intestine. It connects to the stomach at the pylorus at the upper end, and with second part of the small intestine at the jejunum.
51. **Pulmonary hypoplasia**: *Pulmonary*, of, or pertaining to the lungs. *Hypoplasia*, underdevelopment of a tissue or organ. Pulmonary hypoplasia is the underdevelopment of the lungs.

This synopsis, to include the definitions of medical terminology, is intended be an informative tool for those seeking more information about Potter’s Syndrome. The author has given the NPSSG permission to distribute this synopsis as it sees fit.