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Aicardi Syndrome

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Summary

Disease characteristics. Aicardi syndrome is characterized by a classic triad of features: agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Neurologic examination can reveal microcephaly, axial hypotonia, and appendicular hypertonia with spasticity. Moderate- to-severe global developmental delay and mental retardation are expected. Girls with Aicardi syndrome often develop seizures prior to three months and most before one year of age. Ongoing medically refractory epilepsy with a variety of seizure types develops over time. Costovertebral defects are common and can lead to marked scoliosis in up to one third of affected individuals. Other features include characteristic facial features, gastrointestinal difficulties, small hands, vascular malformations and pigmentary lesions of the skin, increased incidence of tumors, lower growth rate after ages seven to nine years, and precocious or delayed puberty. Survival is highly variable, with the mean age of death about 8.3 years and the median age of death about 18.5 years.

Diagnosis/testing. The diagnosis of Aicardi syndrome is based on clinical features including the pathognomonic chorioretinal lacunae identified on ophthalmologic examination, brain magnetic resonance imaging (MRI) findings (dysgenesis of the corpus callosum, gross cerebral asymmetry with polymicrogyria or pachygyria, periventricular and intracortical grey matter heterotopia, choroid plexus papillomas, ventriculomegaly, and intracerebral cysts, often at the 3rd ventricle and in the choroid plexus), and skeletal findings (hemivertebrae, block vertebrae, fused vertebrae, and missing ribs). Aicardi syndrome appears to be an X-linked dominant disorder with lethality in males, but no gene or candidate region on the X-chromosome has been definitively identified and thus molecular genetic testing is not available.

Management. Treatment of Aicardi syndrome is individualized and long-term management by a pediatric neurologist with expertise in management of infantile spasms and medically refractory epilepsy is essential. Individuals with Aicardi syndrome usually require multiple anti-epileptic drugs (AEDs) for adequate seizure control. Some improve with use of vigabatrin and vagus nerve stimulators. Physical therapy, occupational therapy, speech therapy, and vision therapy should begin at diagnosis. Appropriate musculoskeletal support and treatment for prevention of scoliosis-related complications is indicated. Surveillance includes routine dermatologic evaluation to monitor for vascular and other malignancies, monitoring for gastrointestinal complications, and monitoring of the spine to assess the degree of scoliosis.

Genetic counseling. Because Aicardi syndrome is seen only in females and 47,XXY males, it is presumed to be caused by a dominant *de novo* mutation in an X-linked gene with lethality in 46,XY males. The risk to sibs is less than one percent. No instances of mother-to-daughter

transmission have been documented, despite the presence of rare adult women with milder forms of Aicardi syndrome. If a female with Aicardi syndrome conceives, the risk that the mutant allele will be transmitted is 50%; however, male conceptuses with the mutant allele are presumed to be non-viable. Thus at delivery the expected ratio of offspring would be 33% unaffected females, 33% affected females, and 33% unaffected males. Prenatal ultrasound examination or fetal MRI may detect some features of Aicardi syndrome. Prenatal testing is not available by molecular genetic testing as the gene is not known.

Diagnosis

Clinical Diagnosis

The diagnosis of Aicardi syndrome is based on clinical features.

The classically described features of Aicardi syndrome consist of a triad:

- Agenesis of the corpus callosum
- Distinctive chorioretinal lacunae
- Infantile spasms

However, Aicardi syndrome is now recognized to be a more complex neurodevelopmental disorder with additional neuronal and extraneuronal manifestations. Based on these, modified diagnostic criteria have been proposed (Table 1).

Table 1. Diagnostic Criteria for Aicardi Syndrome[1,2]

Classic Triad	Major Features	Supporting Features
Agenesis of the corpus callosum	Cortical malformations (mostly polymicrogyria)	Vertebral and rib abnormalities
Chorioretinal lacunae	Periventricular and subcortical heterotopia	Microphthalmia
Infantile spasms	Cysts around 3rd cerebral ventricle and/or choroid plexus	"Split-brain" EEG
	Optic disc/nerve coloboma or hypoplasia	Gross cerebral hemispheric asymmetry
		Vascular malformations or vascular malignancy

1. The presence of all three classic features is diagnostic for Aicardi syndrome. The existence of two classic features plus at least two other major or supporting features is strongly suggestive of the diagnosis of Aicardi syndrome [Sutton et al 2005].
2. Adapted from Aicardi 1999

Testing

No single laboratory or diagnostic imaging test can definitively establish a diagnosis of Aicardi syndrome. Ophthalmologic examination, brain magnetic resonance imaging (MRI) with and without contrast, electroencephalogram (EEG), and skeletal radiographs should be done to establish the clinical diagnosis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. Aicardi syndrome appears to be an X-linked dominant disorder with lethality in males, but no gene or candidate region on the X-chromosome has been definitively identified.

Several observations support a hypothesis that Aicardi syndrome is caused by de novo mutations of a gene on the X-chromosome that is subject to X-chromosome inactivation [Van den Veyver 2002].

- Nearly all affected individuals are female and, except for one pair of sisters [Molina et al 1989], all reported cases are sporadic.
- At least six pairs of twins that are discordant for Aicardi syndrome are known, five of whom are confirmed dizygotic, which excludes the possibility that the etiology is a prenatal toxin or other disruptive event [Taggard & Menezes 2000].
- The only three known males with a confirmed diagnosis of Aicardi syndrome have a 47,XXY karyotype [Hopkins et al 1979, Aicardi 1999].
- The variable severity and asymmetry of the Aicardi syndrome phenotype could be explained if the putative mutated gene undergoes X-chromosome inactivation [Wettke-Schafer & Kantner 1983]; however, the few limited studies show a general pattern of random X-chromosome inactivation [Wieacker et al 1985, Neidich et al 1990, Hoag et al 1997].
- Because a subset of the clinical findings of Aicardi syndrome - such as the colobomas, agenesis of the corpus callosum, microphthalmia, and seizures - overlaps with those of microphthalmia with linear skin defects syndrome (MLS) and with Goltz syndrome (focal dermal hypoplasia), it was hypothesized that these three conditions were allelic and that the gene for Aicardi syndrome was located on Xp22. However, sequencing and deletion studies now indicate that Aicardi syndrome is likely not allelic to MLS syndrome [Van den Veyver et al 1998, Van den Veyver 2002].
- Until the genetic basis of Aicardi syndrome is known, the possibility remains that Aicardi syndrome is caused by a new mutation on an autosome with gender-limited expression in females.

Testing Strategy for a Proband

Diagnosis depends exclusively on established clinical diagnostic criteria.

Genetically Related (Allelic) Disorders

It is currently unknown if other disorders are allelic to Aicardi syndrome as the causative gene is unknown.

Clinical Description

Natural History

Aicardi syndrome, first described by Aicardi et al (1965), is a neurodevelopmental disorder that affects primarily females [Hopkins et al 1979, Aicardi 1999, Van den Veyver 2002]. Initially it was characterized by a typical triad of agenesis of the corpus callosum, typical chorioretinal lacunae, and infantile spasms [Aicardi et al 1965, Aicardi et al 1969, Donnenfeld et al 1989]. However, as more cases have been ascertained, it has become clear that other neurologic and systemic defects are common. Indeed, not all affected girls have all three features of the classic triad.

Neurologic. The neurologic examination can reveal microcephaly, axial hypotonia, and appendicular hypertonia with spasticity often affecting one side and brisk deep tendon reflexes as well as hemiparesis [unpublished data and Aicardi, 2005]. Moderate-to-severe global developmental delay and mental retardation is expected, but cases with only mild or no learning

disabilities or developmental delay have been reported [Chau et al 2004; Matlary et al 2004; Menezes, Enzenauer et al 1994; Yacoub et al 2003; Prats Vinas et al 2005].

Girls with Aicardi syndrome often develop seizures prior to three months and most before one year of age. Infantile spasms are seen early on, but ongoing medically refractory epilepsy with a variety of seizure types develops over time. Common EEG findings include asynchronous multifocal epileptiform abnormalities with burst suppression and dissociation between the two hemispheres [Fariello et al 1977, Ohtsuki et al 1981].

The MRI reveals dysgenesis of the corpus callosum, which is most often complete, but can be partial [Donnenfeld et al 1989, Aicardi 1999]. Gross cerebral asymmetry with polymicrogyria or pachygyria, periventricular and intracortical grey matter heterotopia, choroid plexus papillomas, and ventriculomegaly and intracerebral cysts, often at the 3rd ventricle and in the choroid plexus, are frequently present [Aicardi 2005].

Ophthalmologic. The pathognomonic chorioretinal lacunae of Aicardi syndrome are white or yellow-white, well-circumscribed, round, depigmented areas of the retinal pigment epithelium and underlying choroid with variably dense pigmentation at their borders (Figure 1) [Donnenfeld et al 1989] that can cluster in the posterior pole of the globe around the optic nerve. The sensory retina overlying the lacunae is usually intact but can be disorganized or entirely absent [Del Pero et al 1986,Menezes et al 1996].

Donnenfeld et al (1989) surveyed ophthalmologists to determine the incidence of various ophthalmologic findings in Aicardi syndrome. While these numbers may be of some help, clinicians should be aware that these data come from multiple ophthalmologists and that historically the chorioretinal lacunae have been the *sine qua non* for the diagnosis of Aicardi syndrome. The reported incidences for the ophthalmologic findings in 18 patients:

- Punched-out chorioretinal lacunae, 100% (18/18)
- Unilateral microphthalmia, 33% (6/18)
- Optic nerve coloboma, 17% (3/18). The colobomas typically involve the optic nerve, choroid, and/or retina, but almost never the iris.
- Nystagmus, 6% (1/18)
- Detached retina, 6% (1/18)

Other ophthalmologic findings include severe optic nerve dysplasia, optic nerve hypoplasia, and persistent fetal vasculature (previously known as persistent hyperplastic primary vitreous). All eye findings can be unilateral or bilateral and asymmetric.

Craniofacial. Characteristic facial features reported in Aicardi syndrome include a short philtrum, prominent premaxilla with resultant upturned nasal tip and decreased angle of the nasal bridge, large ears, and sparse lateral eyebrows [Sutton et al 2005]. Plagiocephaly and facial asymmetry, occasionally with cleft lip and palate (3%), have been reported [McPherson & Jones 1990]. Pierre-Robin sequence has been reported in a single case [Jensen & Christiansen 2004].

Skeletal. Costovertebral defects, such as hemivertebrae, block vertebrae, fused vertebrae, and missing ribs, are common and can lead to marked scoliosis in up to 1/3 of affected individuals [Donnenfeld et al 1989; Menezes, MacGregor et al 1994]. Hip dysplasia has been reported.

Gastrointestinal. Constipation, gastroesophageal reflux, diarrhea, and feeding difficulties are perceived by parents to be the second most difficult problem to manage after seizures [Van den Veyver & Sutton, unpublished observation].

Extremities. Small hands, along with an increased incidence of hand malformations, have been reported [Sutton et al 2005].

Dermatologic. An increased incidence of vascular malformations and pigmentary lesions has been observed [Sutton et al 2005].

Tumors/Malignancies. The incidence of tumors may be increased. The most common tumors are choroid plexus papillomas [Uchiyama et al 1997, Taggard & Menezes 2000, Pianetti et al 2002]; however, lipomas, angiosarcomas, hepatoblastomas, intestinal polyposis, and embryonal carcinomas have also been described [Tanaka et al 1985, Tagawa et al 1989, Tsao et al 1993, Trifiletti et al 1995]. Large-cell medulloblastoma has been reported in a single case [Palmer et al 2004].

Growth. The average heights and weights of girls with Aicardi syndrome closely follow those of the general population up to ages seven and nine years, respectively, after which the growth rate for both height and weight is lower. Growth curves for Aicardi syndrome based on parent survey data have been studied. The weight-versus-height ratio remains similar to the general population [Van den Veyver & Sutton, unpublished observation].

One survey did not document microcephaly, but objective measurements at a single point in time suggest that microcephaly occurs [Sutton & Van den Veyver, unpublished data].

Endocrine. Both precocious puberty and delayed puberty may be present [Van den Veyver & Sutton, unpublished observation].

Survival. Survival in Aicardi syndrome is highly variable and likely depends on the severity of seizures. In a recent survey, the mean age at death was 8.3 years of age, although the median age of death was 18.5 years of age. The ages of death were distributed from less than one year to over 23 years of age. The oldest surviving individual reported in this survey data was 32 years old [Van den Veyver & Sutton, unpublished observation]; a 49-year-old woman with a mild form of the syndrome has been reported [King et al 1998].

Genotype-Phenotype Correlations

No information is available on genotype-phenotype correlations.

Penetrance

Until the gene is identified, the penetrance cannot be established.

Nomenclature

Note: Aicardi syndrome is distinct from Aicardi-Goutières syndrome, an unrelated early-onset encephalopathy characterized by mental and physical handicap associated with calcification of the basal ganglia, particularly the putamen, globus pallidus, and thalamus; leukodystrophy; cerebral atrophy; chronic cerebrospinal fluid (CSF) leukocytosis; and increased concentration of interferon-alpha in the CSF. Inheritance of Aicardi-Goutières syndrome is autosomal recessive. The causative genes are unknown. Approximately 50% of families with Aicardi-Goutières syndrome show linkage to the AGS1 locus on chromosome 3; about 25% show linkage to the AGS2 locus on chromosome 13.

Prevalence

Aicardi syndrome is presumed to be very rare, but the exact prevalence is unknown.

At least 188 persons with Aicardi syndrome in North America and Europe are known [Van den Veyver & Sutton, unpublished observation], but the true prevalence is likely underestimated.

Aicardi syndrome seems to affect all ethnicities equally.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Agenesis of the corpus callosum may occur in isolation or in conjunction with other brain malformations or as part of a larger syndrome. It has been suggested that agenesis of the corpus callosum in association with cysts that do not communicate with the ventricles and the presence of subependymal heterotopia and polymicrogyria are relatively specific for Aicardi syndrome [Barkovich et al 2001].

Neuronal migration disorders , including polymicrogyria (see also the *GeneReview*: Polymicrogyria Overview), pachygyria, and heterotopia (see also the *GeneReview*: X-Linked Periventricular Heterotopia), may occur as isolated malformations or as part of the phenotype associated with other syndromes or chromosome abnormalities.

Oculocerebrocutaneous syndrome (OCCS) characterized by orbital cysts and anophthalmia or microphthalmia, focal skin defects, brain malformations that include polymicrogyria, periventricular nodular heterotopias, enlarged lateral ventricles, and agenesis of the corpus callosum, is predominant in males and has a pathognomonic mid-hindbrain malformation [Moog et al 2005].

Infantile spasms are observed in most girls with Aicardi syndrome, but this type of seizure is not specific for Aicardi syndrome. Infantile spasms may occur in isolation or as part of the phenotype of other syndromes, inborn errors of metabolism, or chromosome disorders. (See also the *GeneReviews*: Tuberous Sclerosis Complex and Rett Syndrome.)

Ophthalmologic findings. Although chorioretinal lacunae are virtually pathognomonic for Aicardi syndrome, they have also been reported in orofaciodigital syndrome type IX (OFD 9) (MIM 258865) [Gurrieri et al 1992].

Microphthalmia and other developmental eye defects may also be seen in other X-linked dominant disorders, such as Goltz syndrome and microphthalmia with linear skin (MLS) defects. However, these two disorders have characteristic skin defects and other features not seen in Aicardi syndrome.

See also the *GeneReview*: Anophthalmia/Microphthalmia Overview.

Management

Evaluations at Initial Diagnosis

- Brain MRI with and without contrast to evaluate for corpus callosum dysgenesis and to search for heterotopias and other evidence of neuronal migration defects
- EEG performed as indicated for seizures and to evaluate the characteristic asynchronous multifocal epileptiform abnormalities with burst suppression and dissociation between the two hemispheres

- Dilated ophthalmologic examination to assess for chorioretinal lacunae and colobomas of the optic nerve, choroid, and retina
- Spine radiographs to assess for scoliosis and segmentation abnormalities of the vertebrae and ribs
- Dermatologic evaluation to look for vascular malformations and pigmentary lesions at risk for malignant transformation
- Clinical genetic and dysmorphology evaluation to confirm mode of inheritance, assess for the presence of craniofacial characteristics, evaluate for related disorders, and provide recurrence risk counseling

Treatment of Manifestations

A pediatric neurologist with expertise in the management of infantile spasms and medically refractory epilepsy is essential for long-term management of seizures.

Individuals with Aicardi syndrome usually require multiple anti-epileptic drugs (AEDs) for adequate seizure control. Improved outcome with vigabatrin [Chau et al 2004] and vagus nerve stimulators have been reported; however, these treatments do not work for all [Van den Veyver & Sutton, unpublished observation].

Physical therapy, occupational therapy, speech therapy, and vision therapy should begin at diagnosis to ensure the best functionality and developmental outcome possible. An individualized therapy plan should be developed and implemented by the therapists and caregivers.

Resection of large choroid plexus papillomas has been reported for management of hydrocephalus [Taggard & Menezes 2000]. Improvement of seizures was also noted in the individual reported. Whether this improvement was related to resolution of the hydrocephalus or whether the choroid plexus papillomas may have been epileptogenic is not clear.

Prevention of Secondary Complications

Spasticity can result in contractures or limited range of motion affecting not only mobility but hygiene care as well. Patients benefit from evaluation by physicians specializing in physical medicine and rehabilitation as well as physical, occupational, and speech therapists.

Costovertebral defects can lead to scoliosis. Appropriate musculoskeletal support and treatment for prevention of scoliosis-related complications is indicated.

Constipation and gastrointestinal problems are frequent and require ongoing management at regular physician visits.

Surveillance

- Routine dermatologic evaluation to monitor for vascular and other malignancies
- Monitoring for and treating gastrointestinal complications at regular physician visits
- Regular monitoring of the spine to assess the degree of scoliosis

Agents/Circumstances to Avoid

None are known.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Because Aicardi syndrome is seen only in females and 47,XXY males, it is presumed to be caused by dominant de novo mutations in an X-linked gene with lethality in 46,XY males.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is not available. —ED.

Parents of a proband

- The parents of a female with Aicardi syndrome are typically unaffected.
- No parent to child transmission has been reported.

Sibs of a proband

- The risk to sibs is less than one percent.
- Only one pair of affected sibs has been reported [Molina et al 1989].
- Five discordant dizygotic twin pairs have been reported [Taggard & Menezes 2000].

Offspring of a proband

- No instances of mother-to-daughter transmission have been documented, despite the presence of rare adult women with milder forms of Aicardi syndrome. This raises the question of whether fertility may be reduced in women with Aicardi syndrome. The hypothesis that fertility in Aicardi syndrome is reduced might also be supported by reports of both precocious puberty and delayed puberty in individuals with Aicardi syndrome [Van den Veyver & Sutton, unpublished observation].
- Theoretically, if a female with Aicardi syndrome conceives, the risk that the mutant allele will be transmitted is 50%; however, male conceptuses with the mutant allele are presumed to be non-viable. Thus, at delivery the expected ratio of offspring would be: 33% unaffected females; 33% affected females; 33% unaffected males.

Other family members of a proband. Aicardi syndrome typically presents as a single case in families, presumably the result of a new mutation. Other family members are usually not at increased risk.

Related Genetic Counseling Issues

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our

understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the gene in which disease-causing mutations occur has not been identified. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal testing is not available by molecular genetic testing as the gene is not known.

Ultrasound examination. Some features detected on prenatal ultrasound examination, such as agenesis of the corpus callosum with intracranial cysts in a female fetus, may raise suspicion for Aicardi syndrome and a number of other developmental brain abnormalities. Use of fetal MRI can be considered in these situations to improve the detection of heterotopia and gyral abnormalities. Other features, such as costovertebral defects and microphthalmia, are more difficult to detect prenatally and are not present in all cases. Definitive prenatal diagnosis of Aicardi syndrome has not been reported in a low-risk case; furthermore, definitive diagnosis of Aicardi syndrome relies on neonatal confirmation of suspected findings and detection of additional features such as chrorioretinal lacunae and seizures [Bromley 2000].

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. OMIM Entries for Aicardi Syndrome

304050	CORPUS CALLOSUM, AGENESIS OF, WITH CHORIORETINAL ABNORMALITY

Molecular Genetic Pathogenesis

No data is available.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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AAL Syndrome d'Aicardi

Aicardi Syndrome Foundation
P.O. Box 3202
St. Charles IL 60174
Phone: 800-374-8518
Email: web@aicardisyndrome.org
www.aicardisyndrome.org

Aicardi Syndrome Newsletter
1510 Polo Fields Court
Louisville KY 40245
Phone: 502-244-9152
Email: newsletter@aicardisyndrome.org
www.aicardisyndrome.org/newsletter

Medline Plus
Aicardi syndrome

National Institute of Neurological Disorders and Stroke
NINDS Aicardi Syndrome Information Page

Aicardi Syndrome International Registry
Phone: 301-230-4674
Email: byk@rti.org
aicardiregistry.rti.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

Aicardi J. Aicardi syndrome. Brain Dev. 2005;27:164–71. [PubMed: 15737696]

Chapter Notes

Author Notes

Dr. Sutton's Web site: www.imgen.bcm.tmc.edu/molgen/facultyaz/sutton.html

Dr. Van den Veyver's Web site: www.imgen.bcm.tmc.edu/molgen/facultyaz/vandenveyver.html

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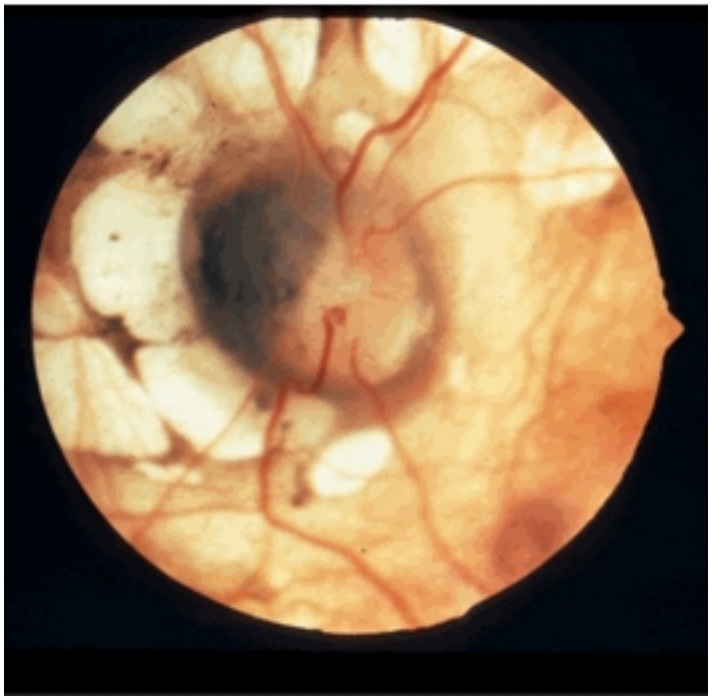

Figure 1. Classic lacunae surround the modestly dysplastic left optic disc. Note the nasal "papilla nigra" appearance and the anomalous branching patterns of the central vasculature.