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Clinical Signs

Cherry-red spot

Suvarna JC, Hajela SA

A cherry-red spot (CRS) at the macula is one of the dramatic diagnostic clues found on fundus examination. It is a clinical sign seen in the context of thickening and loss of transparency of posterior pole of the retina. A useful sign, when clubbed with key clinical features and a good history, it often guides one to the diagnosis of the disease.

Historical Background

Warren Tay (founding member of the British Ophthalmologic Society) provided the first portrayal of the sign in 1881, when he described symmetrical changes in the yellow spot region of each eye in an infant with neurological dysfunction due to Amaurotic Familial Idiocy or Tay Sachs disease.

Clinical Method

The CRS is a fundoscopy finding visualised with a direct ophthalmoscope or by a Slit lamp biomicroscopy. Macula lutea is the small circular area that has a deeper red colour as compared to the rest of the fundus. It is situated about two-disc-diameters (3 mm) temporal to the optic disc, a little below the horizontal meridian. The central 1.5 mm of the macula is the fovea, which, in turn, has the foveola at its centre. The foveola is seen as an intense spot of light in the centre of the macula, due to the reflection of light from the walls of foveal depression.

Direct ophthalmoscopy: The fundoscope is held in the right hand to visualise right eye of the patient by observer’s right eye. The subject is instructed to look straight ahead and examiner approaches the eye with ophthalmoscope from temporal side, so that optic disc is visualised. To visualise the macula, the patient is instructed to look into the light. Slit lamp indirect biomicroscopy: Fundus can be visualised using powerful condensing lens which produces a magnified image.

The CRS is visualised as a bright to dull red spot at the centre of macula, surrounded and accentuated by a greyish white or yellowish halo. Its colour is due to the pigment epithelium and choroid, and therefore may demonstrate colour variability according to the race. Ospina and co-workers have reported a cherry-red spot in a Caucasian child, cherry-brown spot in a Canadian Aboriginal child and cherry-black spot in an East Indian child. Therefore, ‘perifoveal white patch’ rather than ‘CRS’ may be a more appropriate terminology.
The retina has 8-10 layers of ganglion cells. However, macular region (foveola, in particular) is almost devoid of these cells. Diseases associated with accumulation of storage material (such as glycolipids or sphingolipids) in the retinal cellular layers result in swelling and loss of transparency of the multilayered ganglion cells giving it a “white” appearance. The foveola, the thinnest part of the retina being almost devoid of ganglion cells, retains its relative transparency allowing the normal choroidal vasculature to be seen through it.[4,5] These histological features result in the appearance of the central red area (normal foveola) that is surrounded by dull halo resulting from attenuation of transparency of the surrounding area. Later in the course of the disease, ganglion cell death makes the spot less prominent. Atrophy of retinal nerve fibre layer and optic atrophy may also follow.[4,5]

Occlusion of the central retinal artery is also associated with “cherry-red spot”. The fundoscopy reveals a diffuse retinal arteriolo constriction often with visible emboli or blood flow segmentation. The fovea retains its blood supply via the choroidal circulation while the surrounding retina appears milky white due to infarction, intracellular oedema, cellular necrosis and cellular debris accumulation.[6,7] The CRS seen in methanol poisoning is due to macular cystoid oedema[8] and in quinine poisoning due to retinal oedema.[1] In macular hemorrhage, blood which is darker red than the retina contributes to the CRS appearance.[1]

The CRS is associated with inherited metabolic conditions, central retinal artery occlusion (CRAO), orbital contusion and orbital ischemia due to vasospasm. In metabolic disorders, it is seen more consistently in certain conditions like Tay Sachs disease, Sandhoff’s disease and Sialidosis (evident in most cases by the time psychomotor retardation and mental deterioration set in). It may be seen in many cases of Infantile Niemann Pick disease type IA and GM, Gangliosidosis and occasionally in Metachromatic leukodystrophy. Tables 1 and 2 provide information about some of the inherited metabolic disorders associated with CRS. Other conditions associated with CRS include Farber’s disease, Goldberg’s disease, Gaucher’s disease (infantile form), Hunter’s syndrome, Mucopolysaccharidosis VII, Hallervorden Spatz syndrome, Batten-Mayou-Vogt-Spielmeyer syndrome, Spranger’s disease, Cryoglobulinemia and Leber’s congenital amaurosis.[9-11] The CRS varies in its appearance which reflects the differing amounts of substrate and the toxicity of the deposited material.[1] It is opaquely white in Tay Sachs disease and Sandhoff’s disease, faintly gray in Farber’s disease, Metachromatic leukodystrophy and more diffuse in Niemann Pick disease. The opacity correlates with the severity of the visual loss in Tay Sachs and Sandhoff’s disease, in contrast to the normal vision in Farber’s disease.[1] However, late in the course of the disease, the loss of CRS coincides with optic atrophy. In certain cases, however, the loss of vision may be attributed to cortical abnormalities.[1] The CRS has also been reported in quinine, carbon monoxide, methanol and dapsone toxicity.[8,12]

### Table 1: Common inherited disorders associated with Cherry-red spot

<table>
<thead>
<tr>
<th>Inherited disorder associated with Cherry-red spot</th>
<th>Frequency of occurrence</th>
<th>Age of appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM 2 Gangliosidosis type II/Tay Sachs disease</td>
<td>100%</td>
<td>Infancy</td>
</tr>
<tr>
<td>GM 2 Gangliosidosis type II/Sandhoff’s disease</td>
<td>Almost 100%</td>
<td>Infancy</td>
</tr>
<tr>
<td>Sialidosis/Mucolipidosis type I/CRS myoclonus syndrome</td>
<td>100%</td>
<td>Late childhood</td>
</tr>
<tr>
<td>Infantile Niemann-Pick disease type IA</td>
<td>50-100%</td>
<td>Newborn</td>
</tr>
<tr>
<td>GM 1 Gangliosidosis type I/generalized gangliosidosis</td>
<td>50%</td>
<td>Newborn</td>
</tr>
<tr>
<td>Galactosialidosis-early infantile form</td>
<td>-</td>
<td>Newborn</td>
</tr>
<tr>
<td>Galactosialidosis-late infantile form</td>
<td>-</td>
<td>Infancy</td>
</tr>
<tr>
<td>Galactosialidosis-juvenile form</td>
<td>-</td>
<td>Late childhood</td>
</tr>
<tr>
<td>M etachromatic dystrophy</td>
<td>Occasionally</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Distinctive clinical features of common inherited disorders associated with Cherry-red spot

<table>
<thead>
<tr>
<th>Inherited Disorder</th>
<th>Distinctive clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM 2 Gangliosidosis type II/Tay Sachs disease</td>
<td>Infantile onset of exaggerated startle response, hypotonia, later spasticity, convulsions, deafness, blindness</td>
</tr>
<tr>
<td>GM 2 Gangliosidosis type II/Sandhoff’s disease</td>
<td>Manifestations similar to those seen in Tay Sachs disease</td>
</tr>
<tr>
<td>Sialidosis/Mucolipidosis type I/CRS myoclonus syndrome</td>
<td>Onset in childhood and early adulthood. Debilitating myoclonic seizures, sometimes movement disorders in second decade, progressive visual loss, nyctagmus, ataxia, seizures Intelligence usually preserved somatic features usually absent</td>
</tr>
<tr>
<td>Infantile Niemann-Pick disease type IA</td>
<td>Infantile onset. Relentlessly progressive psychomotor retardation, failure to thrive, hepatosplenomegaly, interstitial pneumonia, vacuolated lymphocytes</td>
</tr>
<tr>
<td>GM 1 Gangliosidosis type I/Generalized Gangliosidosis</td>
<td>Neonatal or infantile onset. Coarse features, bone changes like mucopolysaccharidosis, hepatosplenomegaly, oedema, ascites, blindness, exaggerated startle response, seizures, psychomotor retardation</td>
</tr>
<tr>
<td>Galactosialidosis- early infantile form</td>
<td>Infantile onset. Coarse features with dysostosis (Hurler-like phenotype), hepatosplenomegaly, edema, ascites, renal failure, early blindness and development delay</td>
</tr>
<tr>
<td>Galactosialidosis-late infantile form</td>
<td>Similar to early infantile type with mild developmental delay</td>
</tr>
<tr>
<td>Galactosialidosis-juvenile form</td>
<td>Insidious onset in late childhood or early adulthood with dysmorphism, angiokeratoma, dysostosis multiple corneal opacities and psychomotor retardation</td>
</tr>
</tbody>
</table>
The CRAO presents with sudden onset painless profound unilateral visual loss. Emboli may not be visible if they lodge prior to lamina cribrosa. The condition was first reported by von Graefe in 1859. Fluorescein angiography shows filling of the choroid and ciliary branches perfusing the optic nerve head, while displaying delayed retinal arterial filling and prolongation of the arteriovenous circulation time. One can determine the etiology of occlusion if the embolus is visualised: Cholesterol-laden emboli have a refractile yellowish appearance; the presence of dusky grey emboli suggests platelet and fibrin aggregation, while the presence of white emboli suggests calcification arising from carotid arteries or cardiac valves. Conditions that pre-dispose to CRAO include retinal emboli due to endogenous or exogenous source; hypertension, diabetes mellitus, carotid occlusive disease, cardiac valvular disease, atheromatous vascular disease, arteriosclerotic vascular disease, vasculitic syndromes (temporal arteritis, SLE, etc.), blood dyscrasias (e.g., sickle hemoglobinopathy), hypercoagulable states (e.g., antiphospholipid antibodies), sepsis and DIC, vasospasm, vascular compression, cervical trauma with carotid artery dissection, intravenous drug use and migraine. In the natural history of CRAO, patients have persistent severe visual loss, an afferent pupillary defect and later optic atrophy. Some patients may regain useful vision. Rubeosis of iris and neovascular glaucoma develops in less than 5% cases.

**Causes of CRS-like lesions** and pseudo CRS

Certain illnesses are associated with macular lesions resembling a CRS. These include:

1. Adult Niemann Pick disease (ring of perifoveal crystalloid deposits)
2. Gaucher’s disease (atypical macular CRS)
3. Lactosyl ceramidosis (increasing redness of macula)
4. Sea blue histiocyte syndrome (perifoveal yellowish white scintillating granules in doughnut shaped pattern)

Conditions like macular haemorrhage or macular hole with retinal detachment could be considered as pseudo-CRS, because the abnormality is in the foveola rather than parafoveal area.

**Approach to Diagnosis and Management**

In children, metabolic diseases constitute the commonest cause for CRS. The exact metabolic or storage disease can be diagnosed on the basis of age of onset, associated manifestations, inheritance pattern; diagnostic evaluation carried out in the affected sib, if any and the results of relevant laboratory investigations. In newborns, hepatosplenomegaly with vacuolated lymphocytes would suggest GM1 Gangliosidosis, Niemann Pick disease type IA or early infantile Galectosialidosis. An additional finding of coarse facies, bone changes, oedema with ascites would favour GM1 Gangliosidosis or early Infantile Galectosialidosis; whereas, interstitial pneumonia and neurologic deterioration would suggest Niemann Pick disease type IA disease. In infancy, exaggerated startle response, hepatosplenomegaly, myoclonic jerks, hypotonia and neuroregression would suggest a diagnosis of GM2 Gangliosidosis type 1 (Tay Sachs disease) or type 2 (Sandhoff’s disease), whereas hepatosplenomegaly with bone changes would favour a diagnosis of late infantile Galectosialidosis. In late childhood, blindness and progressive myoclonic jerks suggest Sialidosis (CRS Myoclonus syndrome) whereas bone changes, dysmorphism, angiokeratoma, corneal opacities and psychomotor retardation would suggest juvenile Galectosialidosis.

The CRS is seen bilaterally in metabolic disorders, quinine and other drug toxicity and Leber’s congenital amaurosis; whereas, it is seen unilaterally in most cases of CRAO orbital contusions, macular hole with retinal detachment or macular haemorrhage.

The CRS is more commonly associated with CRAO in adults. The age, health of patient, history of trauma or vascular disease and unilaterality of lesion may help to distinguish it from the metabolic disorders. In such instances providing emergency management and treating the underlying disorders or risk factors constitute vital therapeutic interventions. In children with CRAO haemoglobinopathies like sickle cell disease, hypercoagulable states like antiphospholipid antibodies and vasculitis due to systemic lupus erythematosus are more common causes whereas in adults two-thirds of all patients with CRAO have associated hypertension, one-fourth have carotid occlusive disease, diabetes or cardiac valvular disease or a combination. Bilateral affection is rare and suggestive of arteritic disease.

Several inherited metabolic diseases have no definitive treatment. However, early diagnosis allows for appropriate counseling and prenatal diagnosis (For example, determination of levels of Hexosaminidase A and B levels in Sandhoff’s disease). CRAO, an ophthalmic emergency should be treated within 24 h. Medical and surgical lowering of intraocular pressure, carbon dioxide rebreathing, steroids (in vasculitis), vasodilator drugs, hyperbaric oxygen, anti-fibrinolytic drugs, barbiturate coma, free radical scavengers and antioxidants have been tried with variable results.

**Importance of CRS**

It should be appreciated that CRS is not a disease condition in itself, but an ophthalmoscopic evidence of pathology that may involve the peripheral layers of the retina and multiple systems of the human body. Detection of CRS can aid in short-listing certain conditions followed by their speedy correct diagnosis. Although CRS may be seen in certain conditions with full-blown clinical picture, detection of CRS prior to clinical manifestation, e.g., in Sialidosis (CRS may be seen without clinical features) may aid in early diagnosis, prognostication and proper counseling.

**References**


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