X-linked hydrocephalus

General information

Inherited hydrocephalus (HCP) with phenotypic expression in males, passed on through carrier mothers who are phenotypically normal. Classical phenotypic expression will skip single generations.

Incidence: 1/25,000 to 1/60,000.

Prevalence: ≈ 2 cases per 100 cases of hydrocephalus.

Gene located on Xq28.

Pathophysiology

L1CAM membrane-bound receptor plays a significant role in CNS development for axonal migration to appropriate target locations through Integrin cell adhesion molecules and MAP Kinase signal cascade.

Abnormal gene expression results in poor differentiation and maturation of cortical neurons, macroscopic anatomical abnormalities (bilateral absence of pyramidal tracts, see below). Cytoplasmic domain loss of function mutations result in severe L1 syndrome, whereas mutations retaining expression of some functional protein (component imbedded in cell membrane) leads to mild L1 syndrome.

L1 syndromes

Classical syndromes include CRASH (corpus callosum hypoplasia, retardation, adducted thumbs (clasp thumbs), spastic paralysis, HCP), MASA (mental handicap, aphasia, shuffling gait, adducted thumbs), and HSAS (HCP with stenosis of the aqueduct of sylvius). Spectrum of disease also includes x-linked agenesis of the corpus callosum (ACC), and spastic paraparesis type 1.

Recent deliniations:

● mild L1 syndrome: adducted thumbs, spastic paralysis, hypoplasia of CC

● severe L1 syndrome: as in mild L1 syndrome plus anterior cerebellar vermis hypoplasia, large massa intermedia, enlarged quadrigeminal plate, rippled ventricular wall following ventriculoperitoneal shunt placement (pathognomonic for X-linked HCP). Profound mental retardation in virtually all cases

Radiographic findings likely present if severe L1

1. severe symmetric HCP with predominant posterior horn dilation

2. hypoplastic CC/ACC

3. hypoplastic anterior cerebellar vermis

4. large massa intermedia

5. large quadrigeminal plate

6. rippled ventricular wall following VP shunt placement (pathognomonic)

Treatment

No intervention demonstrates improvement in retardation status in observational papers.

1. VP shunt: main purpose is management of head size for improved care by caregiver. Does not improve neurologic outcome

2. there are no current genetic therapies for L1CAM protein abnormalities

3. prenatal U/S: early (≈ 20–24 weeks gestational age) with frequent repeat scan in known carrier mothers. May allow for medically indicated termination early on

4. male infants with HCP and ≥ 2 clinical/radiographic signs should undergo genetic testing for L1CAM mutation detection for future pregnancy counseling.