

# Alexander's disease

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## Abstract

*Alexander's disease, a neurodegenerative disorder, was identified in 1949 on the basis of neurohistological criteria, i.e., the presence of dystrophic astrocytes containing intermediate filament aggregates (Rosenthal fibers) associated with myelin abnormalities. Since then, different clinical forms have been individualized. The infantile form (birth to 2 years), the most common, is characterized by its early onset and severe evolution. Its symptomatology associates progressive megalencephaly (sometimes hydrocephaly), retarded psychomotor development or mental deterioration, pyramidal signs, ataxia and convulsive seizures. Computed tomography scan and magnetic resonance imaging suggest the diagnosis by revealing white matter anomalies, predominantly in the frontal lobes. Juvenile forms start in school-aged children and associate spastic paraplegia and progressive bulbar signs. Adult forms are heterogeneous and difficult to diagnose. This rare disease, often considered to be a leukodystrophy, is usually sporadic; only a few familial cases have been reported. The discovery of Rosenthal fibers in transgenic mice overexpressing human glial fibrillary acidic protein (GFAP), which is the main intermediate filament of astrocyte, led to the search for mutations in its encoding gene. More than 20 GFAP mutations have been reported; they are de novo dominant mutations. However, a prenatal diagnosis seems desirable in light of the risk of germinal/germ-cell mosaicism. At present, treatment is purely symptomatic.*

## Keywords

Alexander's disease, astrocyte, Rosenthal fibers, glial fibrillary acidic protein (GFAP), myelin, leukodystrophy

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## Name of the disease and its synonyms

Alexander's disease or leukodystrophy with Rosenthal fibers (RF)

common neurohistological criteria have been identified: presence of RF associated with a myelin deficit of varying intensity.

## Diagnostic criteria

Since its first description in 1949 by W.S. Alexander (1), different clinical forms with

The diagnosis of infantile and juvenile forms is suggested by a group of clinical and radiological signs, and confirmed by histological examination of a cerebral biopsy or postmortem (2-6).

The diagnosis of adult forms relies primarily on histology because the neurological signs are poorly specific or even absent.

The presence of mutations in the gene coding for glial fibrillary acidic protein (*GFAP*) now provides confirmation of the diagnosis but it is still too early to affirm that all the cases; especially adult forms are linked to abnormalities of this gene (7).

#### Differential diagnosis/excluded diseases

The infantile forms require the consideration of progressive encephalopathies with macrocephaly and hydrocephalies but sometimes only mental retardation at onset. After a neuroradiological work-up, the diagnosis is that of leukoencephalopathy with macrocranium. Thus, [Canavan's disease](#) (dosage of N-acetylaspartate) and [megalencephalic leukodystrophy with cysts](#) (8, 9) have to be eliminated. In the absence of diagnostic certitude, the prognosis should be announced with caution because leukodystrophy with megalencephaly and minor symptoms has been reported in the literature (10).

Later-onset forms are even more difficult to diagnose; progressive bulbar involvement in the juvenile forms and primarily multiple sclerosis in adults have to be excluded.

#### Incidence

Alexander's disease is very rare.

#### Clinical description

Different clinical forms have been identified (2-5).

- **The infantile forms** (birth to 2 years) have an early onset, around 6 months, and their prognosis is poor, with most patients dying during childhood. The symptomatology associates abnormal psychomotor development (retardation or stagnation and then deterioration), progressive megalencephaly and/or hydrocephaly, a pyramidal syndrome, ataxia and epileptic seizures. Episodes of deterioration with vomiting can occur during the course of the disease, leading to a search for intracranial hypertension. Elevated protein concentrations are sometimes found in the cerebrospinal fluid. Computed tomography (CT) scans and magnetic resonance imaging (MRI) show anomalies of hemispheric white matter, sometimes cavitated, which predominate in the frontal lobe. They are often associated with lesions in the pontine nuclei, thalamus and cerebellum. All these anomalies are enhanced with contrast medium (6).

- **The juvenile forms** start in school-age children, on the average around 9.5 years, and the duration of their evolution varies (from 15 months to more than 12 years). The symptomatology differs from that of the infantile form and consists mainly of spastic paraplegia and progressive bulbar signs; cognitive functions are usually spared.
- **The adult forms** are heterogeneous. Most of the patients have relapsing neurological symptoms suggestive of multiple sclerosis. For the majority of patients, the diagnosis is evoked only once the neurohistological examination has identified the presence of RF. In some adults, without neurological symptoms, who died of complex systemic diseases, the presence of RF raised the possibility of Alexander's disease but, for most authors, these patients were representative of a distinct entity.

#### Etiology

The histological aspect of the central nervous system served as the basis for the description of this entity (1): a proliferation and then degeneration of astrocytes, a myelin deficit, and the presence of RF (intra-astrocytic osmiophilic eosinophilic hyalin deposits) predominantly localized in the subependymal, subpial and perivascular areas. When this pathology was described, it was considered a primary disease of astrocytes (1). However, RF are not specific to it, as they can be seen in [astrocytic tumors](#), [Bourneville's disease](#), focal cortical dysplasias, [hemimegalencephaly](#), [multiple sclerosis](#)... but their abundance, distribution and association with an intense and diffuse myelin deficit are characteristic of Alexander's disease.

Because Alexander's disease is rare and usually sporadic, the search for its etiology is difficult and is focused on the biochemical analysis of RF, the main marker of the disease. The primary component of RF is the protein alphaB-crystallin, which is associated with heat shock protein (hsp) 27, ubiquitin and GFAP. Because alphaB-crystallin and hsp27 are stress proteins, some authors have hypothesized that RF appear in response to chronic stress linked to an unknown stimulus (11). However, to study astrogliosis in 1998, Messing *et al.* (12) created a transgenic mouse that overexpresses human GFAP and whose central nervous system contains RF. Thus, the *GFAP* gene became a prime etiological candidate for Alexander's disease. More than 20 *GFAP* mutations have been since reported; they are *de novo* dominant mutations (13). Nevertheless, *GFAP* null mice display myelin abnormalities and blood-brain barrier dysfunction that are present in Alexander

disease. Given the pivotal role of astrocytes in brain physiology, there are many possibilities for astrocytes to dysfunction and to impair the functions of other cells.

Although no *GFAP* mutation was found in one patient's coding sequence, the disease could be the consequence of a mutation in the promotor or gene rearrangement. However, the involvement of another gene, especially in the atypical and adult forms, cannot be excluded at the present time.

#### **Genetic counseling/Prenatal diagnosis**

The disease is usually sporadic but several very rare familial cases have been described with the involvement of several members of the same kindred. Those cases were infantile forms and dominant adult forms. All studied patients with mutated *GFAP* have been associated with sporadic events, but the existence of gonadal mosaicism cannot be excluded. At present, we propose looking for the mutation identified in the index case at the time of another pregnancy.

#### **Management and treatment**

At present, treatment is purely symptomatic.

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