CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) is caused by mutations in the Notch3 gene (chromosome 19q12).\(^1\) Patients present with stroke-like episodes which occur at a mean age of 45 years (range 27-65).\(^1\) Symptoms also include migraine and dementia. The Central Coast of NSW, with a population of 285,000, has approximately 1000 stroke cases each year; some presumably due to CADASIL. CADASIL is diagnosed using electron microscopy (EM) to detect characteristic deposits adjacent to the perivascular cells of arterioles.\(^3\) Here, we report our experience using this strategy during the period 1999-2002.

## METHOD

Forty-seven patients were screened. Criteria included: (1) stroke at a young age; (2) migraine; (3) MRI changes consistent with leucoencephalopathy or subcortical strokes; (4) cognitive decline or dementia and; (5) a family history with clinical features suggestive of CADASIL.

A skin biopsy was taken from each patient at a Central Coast neurology clinic. The tissue was fixed in glutaraldehyde then sent to the EM Unit at SouthPath (Flinders Medical Centre, Adelaide) where it was processed for EM using standard techniques.\(^4\) Approximately fifty blood vessels in each biopsy were evaluated by EM for the presence of typical CADASIL deposits at a magnification of ~5-15,000X.\(^3\) “Typical” deposits were defined as extracellular dense, granular deposits sited in an indentation of the perivascular cell membrane, or closely associated with the membrane.\(^3\)

## CASE HISTORY - Patient ‘A’

A 41-year-old male with a family history of multi-infarct dementia and cerebrovascular disease (Figure 3) presented with an episode of paraesthesia and numbness involving his left hand, arm and leg. In addition, the patient was disoriented and had blurred vision. An episode of disorientation and confusion had also occurred 5 months earlier. An MRI (Figure 4) showed multiple areas of increased signal intensity in the periventricular and subcortical white matter bilaterally. A skin biopsy was performed and typical CADASIL deposits were identified by EM (Figure 5).

## RESULTS

Six (13%) of the 47 patients who had a skin biopsy were diagnosed as positive for CADASIL by EM (Figure 1). The most salient clinical features associated with the positive cases were stroke, MRI changes, cognitive decline/dementia and family history (Figure 2). Patients tested ranged in age from 21 to 78. The mean age of positive patients was 49.5 years (range 21-78 years). There was no significant difference between the ages of the positive and negative groups (t-test for equality of means).

## CONCLUSION

- CADASIL screening should be considered in younger patients presenting with stroke, an abnormal MRI, cognitive decline/dementia and/or a family history suggestive of CADASIL.
- Patients diagnosed as CADASIL-positive by EM may present with recognised clinical features and associated findings but, not all have a positive family history and may be ‘de novo’ cases.\(^3\)
- Diagnosis of CADASIL by EM is complex. Deposits similar to CADASIL can be found in patients with hypertension and diabetes mellitus. CADASIL may be over-diagnosed unless strict criteria are used for EM evaluation.
- Positive EM diagnosis should be restricted to cases where the deposits and their localisation to perivascular cells are typical of CADASIL.
- Cases may be divided into: (1) those typical of CADASIL; (2) those that are negative, and; (3) an indeterminate group that require clinicopathological correlation and genetic testing.
- In this framework, EM appears to represent a useful and rapid screening method for CADASIL.

## References


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