STROKE EXPERT SYSTEM EXTENDED TO DIAGNOSIS CADASIL

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ABSTRACT

BACKGROUND: A stroke diagnosis expert system prototype StrokeDx has been developed. StrokeDx has been extended to include knowledge about a genetic stroke syndrome, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). A clinical discovery of 2 new CADASIL mutations is reported. Mutation 1 is a G to T transversion at nucleotide position 2077 with an amino acid substitution glycine to cysteine. Mutation 2 is a C to T transversion at nucleotide position 2227 with an amino acid substitution arginine to cysteine. CADASIL is frequently misdiagnosed and software tools to aid diagnosis are required. GOAL: Augment StrokeDx with knowledge (clinical, genetics, examination, MRI analysis) about CADASIL. METHODS: A new CADASIL specific rule set was encoded using the StrokeDx prolog-like system. Test case data were analyzed by StrokeDx. RESULTS: StrokeDx computed diagnostic confidence factor of 1.0 for the CADASIL case and computed much lower factors for other non-CADASIL strokes. CONCLUSIONS: Stroke Dx has demonstrated technical flexibility, encoding of CADASIL-specific rules was efficient, and the resulting expert system is more powerful AI system.

KEY WORDS

STROKE, EXPERT SYSTEM, CADASIL, NEUROLOGY

1. Introduction

CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) may manifest as migraine with aura, ischemic attacks, cognitive decline, and psychiatric symptoms [1]. CADASIL is caused by a mutation in the *Notch3* transmembrane receptor gene. Almost all of the known mutations associated with CADASIL result in a gain or loss of a cysteine residue within the extracellular portion of the *Notch3* receptor, where all 34 EGF-like repeats are situated. The cysteine residue change alters disulfide bonds and disrupts proper folding of the protein [2]. Disruption of the Notch3 receptor gene leads to degeneration of vascular smooth muscle cells (VSMC) and results in thickening, fibrosis, and luminal narrowing in small and medium-sized arteries [1,2]. Accumulation of granular osmiophilic material (GOM) between VSMC is noted and GOM may be partially composed of *Notch3* extracellular domain [2]. White matter hyperintensities are usually seen in T2W and FLAIR MRI imaging [1]. This disorder is frequently misdiagnosed as either multiple sclerosis or stroke.

StrokeDx: The expert system StrokeDx has been previously reported (Sponsler [4]). This system encodes knowledge as rules using a logic programming tool Prolisp. Prolisp is based on Prolog [5]. A diagnosis driven backward-chaining algorithm is employed to compute confidence factors. The initial application of Prolisp was for epilepsy syndrome diagnosis [3]. Recent work involves diagnosis of stroke syndromes. The goal and development described in this report are centered on the disorder CADASIL.

2. Case Information

A 49-year-old, right-handed Caucasian male with no prior medical conditions presented to the emergency department with right sided weakness. Patient had no prior medical diagnoses. A head CT revealed extensive bilateral white matter disease suggestive of a demyelinating process or vasculitis. The neurological examination demonstrated dysarthria, right facial weakness, right grip weakness (grade 4+), right leg weakness (grade 4+), and abnormal coordination of right hand and right leg. Babinski sign was absent. Reflexes were symmetrical and normal except for absent ankle jerks. Sensory examination was unremarkable. Cardiac enzymes were negative and routine ER labs were unremarkable, except for a blood glucose of 110 and 5% eosinophils on the CBC differential. The patient was admitted and a brain MRI demonstrated extensive severe white matter hyperintensities on T2 weighted and fluid attenuated inversion recovery (FLAIR) sequences. Signal changes were seen in the basal ganglia, cerebral peduncles, and pons. Lacunar infarcts were seen in the pons and basal ganglia. A CT angiogram demonstrated a

hypoplastic right vertebral artery. MRI images of the cervical and thoracic spine revealed no disk or cord disease (Figure 1). Cerebrospinal fluid showed WBC 0, RBC 1, was Gram stain negative and negative for fungus, herpes simplex virus (HSV), and viral cultures. Echocardiogram showed normal ejection fraction, normal valves, and no patent foramen ovale.

The patient was treated for presumptive multiple sclerosis (MS) with a five day course of IV methylprednisolone (1 gram). Patient experienced only minimal improvement in symptoms despite aggressive corticosteroid treatments (casting some doubt on diagnosis MS).
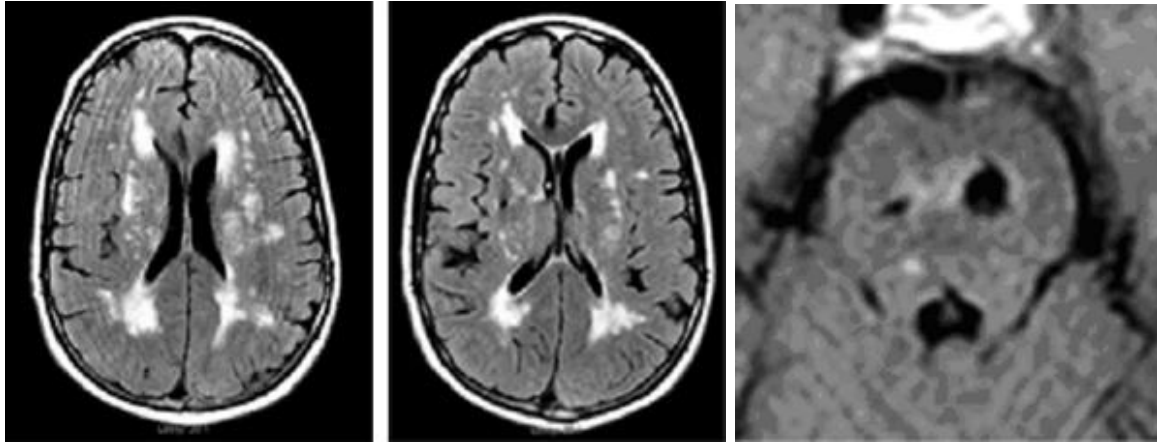

Figure 1. MRI analysis reveals extensive white matter FLAIR hyperintensities (images on left), subcortical infarcts in the pons (image on right).

Genetic Analysis Reveals Two Novel Mutations in Notch3

A blood sample was sent to Athena Diagnostics for genetics analysis with the hypothesis that the patient had CADASIL. DNA analysis demonstrated **two novel mutations** of the *Notch3* gene not previously reported. Both mutations were predicted to significantly alter the structure and function of any of the EGF-like repeat domains of the *Notch3* receptor, according to the Diagnosis Service Report [3]. Mutation 1 is a G to T transversion at nucleotide position 2077 (codon 667) with an amino acid substitution glycine to cysteine. Mutation 2 is a C to T transversion at nucleotide position 2227 (codon 717) with an amino acid substitution arginine to cysteine [6].

Skin Biopsy Results Include Granular Osmiophilic Material

Ultrastructural examination of several small blood vessels showed electron dense, granular material external to the muscular coat of the vessels. These were described as *electron dense extravascular deposits*, consistent with CADASIL [7]. The electron dense extravascular deposits are also known as GOM in the literature [2].
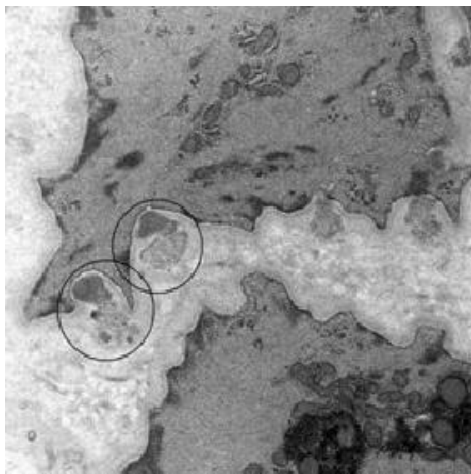

Figure 2. Electron micrograph reveals granular osmiophilic material (GOM) which is circled.

New Cadasil Mutation is Reported

Based on the clinical history, MRI images, DNA analysis revealing two *Notch3* mutations involving addition of cysteine residues, and skin biopsy showing electron dense extravascular deposits, we propose that our patient has the disorder called CADASIL and that the mutations (noted above) be added to the medical genetics literature as CADASIL mutations.

3. StrokeDx Extended for CADASIL Stroke Syndrome

The StrokeDx system was augmented using new rules specific to CADASIL. The authors believe that this new knowledge will make StrokeDx a more powerful diagnostic system.

CADASIL has clinic features that are similar to stroke (and multiple sclerosis). CADASIL does differ clinically: there is a particular MRI pattern, there is non-response to standard stroke and MS treatments, there is strong family history of dementia and migraines. Patient symptoms might include migraines, memory loss, weakness, sensory deficits. Patient examination may reveal weakness in any extremity, sensory loss in any extremity, upper motor neuron signs, dementia. MRI images show extensive white matter changes especially in the anterior temporal lobes. MRI images demonstrate subcortical infarcts. MR angiography may be normal (CADASIL affects arterioles not large or median arteries). DNA analysis demonstrates cysteine related mutation in the Notch 3 gene on chromosome 19. Ultrastructural analysis of skin biopsy typically reveals *granular osmiophilic material* (GOM). These clinical features were encoded as rules in StrokeDx.

Rule Definition: CADASIL

In the following examples, the function define-rule and define-rule-and-default are used. Each Prolisp pattern has the structure (functor arg1 arg2 arg3). *Functor* names the predicate for the pattern. Prolisp variables are marked with a question mark prefix (?stroke-cf for example). A pattern constant will have no question mark ("severe", for example). In the following rule definition, the pattern (CADASIL ?CADASIL-CF) is the diagnostic hypothesis. Proof by deductive retrieval will bind the variables. ?CADASIL-CF is the resulting confidence factor.

```
(define-rule
'(CADASIL  ?CADASIL-CF)
'((has-white-matter-disease  temporal  :left  ?wm-
temporal-left-cf  ?wm-temporal-left-trace)
(has-white-matter-disease  temporal  :right  ?wm-
temporal-right-cf  ?wm-temporal-right-trace)
(has-dementia  ?dementia-cf  ?dementia-trace)
(has-migraines  ?migraines-cf  ?migraines-trace)
```

```
(has-family-hx-dementia  ?family-dementia-cf  ?family-
dementia-trace)
(has-family-hx-migraines  ?family-migraines-cf  ?family-
migraines-trace)
(has-family-hx-strokes  ?family-strokes-cf  ?family-
strokes-trace)
(has-gom  ?gom-cf  ?gom-trace)
(has-notch3  ?notch3-cf  ?notch3-trace)
(average4  ?wm-temporal-left-cf  ?wm-temporal-right-cf
?dementia-cf  ?migraines-cf  ?cf1)
(average4  ?family-dementia-cf  ?family-migraines-cf
?gom-cf  ?notch3-cf  ?cf2)
(average2  ?cf1  ?cf2  ?cadasil-cf))
```

Benchmark Dataset for CADASIL

A CADASIL benchmark dataset was manually constructed. The benchmark included patient symptoms, patient examination signs, MRI data, skin biopsy ultrastructural results, and DNA analysis of the Notch3 gene. The benchmark included these elements: weakness of right arm and right leg, migraine history, MRI showing severe white matter signal changes including temporal lobes, family history of migraines, early strokes, and dementia, skin biopsy showing granular osmiophilic material, DNA analysis showing cysteine related mutations in Notch3 gene of chromosome 19. StrokeDx CADASIL rules were next created based on the knowledge about CADASIL and the benchmark dataset.

CADASIL Benchmark vs. Stroke Rules

The StrokeDx system (frontal stroke, occipital stroke, Wallenberg stroke, radial neuropathy, and CADASIL) were applied to the CADASIL benchmark. StrokeDx computes a diagnostic confidence factor (DCF) for each rule set. Confidence factor of 0 represents false, 0.5 represents unknown, and 1.0 represent true diagnosis. The results are included in Table 1.

StrokeDx Testing and Results

Table 1 contains data from StrokeDX testing. The CADASIL rule achieved the highest CF and this is the correct (and expected) diagnosis. Other stroke rules (frontal, occipital, and Wallenberg) scored either close to zero or uknown. The radial neuropathy rules query for negative frontal MRI stroke sign and since the CADASIL benchmark is negative for frontal strokes, score is moved toward 1. The radial neuropathy rules do not (yet) include rules for white matter signal changes and so confidence is not decreased by the presence in the benchmark of white matter changes. White matter MRI abnormalities ("leukoencephalopathy") are highly suggestive of CADASIL (and also multiple sclerosis) and stroke rules must be adjusted for white matter changes (by having scores lowered).

DIAGNOSIS	Confidence Factor	Notes
Left Frontal Stroke	0.33	Negative for frontal stroke on MRI
Right Frontal Stroke	0.5	Negative for frontal stroke on MRI
Left Occipital Stroke	0.2	Negative for occipital stroke on MRI
Right Occipital Stroke	0.2	Negative for occipital stroke on MRI
Right Wallenberg Stroke	0.0	Negative for ptosis, meiosis, anhidrosis
Left Wallenberg Stroke	0.0	Negative for ptosis, meiosis, anhidrosis
Left Radial Neuropathy	0.75	Negative for frontal stroke; no rules for MRI infarcts or white matter changes
Right Radial Neuropathy	0.75	Negative for frontal stroke; no rules for MRI infarcts or white matter changes
CADASIL	**1.0**	Migraines, dementia, genetics, subcortical infarcts, white matter changes +

Table 1. CADASIL Benchmark vs. all Stroke Rules. The CADASIL rule achieved the highest CF and this is the correct diagnosis. The radial neuropathy rules query for frontal MRI stroke sign and since the CADASIL benchmark is negative for frontal strokes, score is moved toward 1. The radial neuropathy rules do not yet include rules for white matter signal changes and so confidence is not decreased by the presence in the benchmark of white matter changes.

4. Discussion

The authors propose that this report contributes importantly to scientific literature for these reasons. (1) There are no AI systems reported that diagnose this rare genetic stroke syndrome. (2) The case discussed in our paper carries a novel CADASIL Notch3 mutation (that has not been previously documented). (3) The ease of adding CADASIL rules to the diagnostic engine represents the robust nature of the StrokeDx Architecture.

The CADASIL disorder is a rare genetic stroke/dementia disorder and is misdiagnosed (as multiple sclerosis or stroke). Treatment of CADASIL with multiple sclerosis medications (glucocorticoids or beta1a interferon) or stroke prevention medications would be ineffective and inappropriate. Encoding the knowledge for detecting CADASIL is important for a stroke diagnostic system. StrokeDx rules encode CADASIL-specific history, examination, MRI findings, family history, and DNA analysis. If there is missing data (DNA analysis for example), default values are used; other positive patient data would tend to carry CADASIL hypothesis to the top of a sorted diagnosis list and encourage the clinician to do the DNA analysis for the Notch3 mutation. The authors do not believe there are any stroke expert systems in research currently and none with CADASIL specific knowledge. This system is unique and moving medical information systems in a forward direction. To develop the high level CADASIL diagnosis rule, many subsidiary rules (for family history, migraines, dementia) were created. These rules can be used in other high level diagnosis rule trees (due to the fundamental pattern matching behavior of logic programming language used in this system).

Competition Between Diagnoses Is Based on Confidence Factors.

There are other diagnoses that would partially match the CADASIL rules. These include migraines, dementia, multiple sclerosis, ischemic stroke, vasculitis, and cerebral hemorrhage. We have not yet included these disorders into StrokeDx but that work is in the design phase. When the StrokeDx rule library is more complete, the system will compute confidence factors (as described above) and the CADASIL hypothesis will compete with other diseases based on computed factors. StrokeDx rules can either yield confidence factor close to zero (representing "the diagnosis is not correct") or a CF close to one (representing "the diagnosis is correct").

CADASIL vs. ischemic stroke. An ischemic stroke diagnosis rule library would exclude CADASIL if there are no migraines, no family history of migraines, no family history of dementia, and no patient dementia. The CADASIL rule has an exclusionary criterion specifically the absence of a large vessel occlusion (such as the posterior cerebral artery). Even in the absence of genetic findings for CADASIL, other subsidiary rules will support the CADASIL over stroke diagnosis. Our evaluation (as reported above) discriminates between ischemic stroke and CADASIL (see Table 1).

CADASIL vs. multiple sclerosis. A multiple sclerosis (MS) rule will have CADASIL exclusionary criteria including the absence of subcortical infarcts, no dementia, few migraines, and no family history of migraines. There

are MRI lesion patterns that also differentiate between MS (per-ventricular lesions) and CADASIL (temporal lobe lesions) [1]. MS rule library design calls for cerebrospinal fluid analysis and such subsidiary rules will be incorporated into the diagnosis of ischemic stroke and CADASIL as exclusionary. Elevated IgG Index and IgG Synthesis rate support the diagnosis of MS [9]. The MS rule library is in the design phase and not yet implemented. The authors believe that the StrokeDx framework will easily support new knowledge of MS.

CADASIL vs. dementia. Dementia rules would exclude MRI subcortical infarcts, frequent migraines, family history of migraines. CADASIL rules will compete against the dementia rules when MRI shows infarcts, frequent migraines are present, and family history of migraines/dementia are present. The dementia rule library is in the design phase and not yet implemented. The authors believe that the StrokeDx framework will easily support new knowledge of dementia.

5. Conclusions

This report documents (a) a patient with two novel Notch3 CADASIL mutations and (b) the successful extension of StrokeDx expert system for the CADASIL disorder.

The new Notch3 mutations (chromosome 19) will be added to the database of all such mutations and support laboratory confirmation of the disorder for future cases. Mutation 1 is a G to T transversion at nucleotide position 2077 (codon 667) with an amino acid substitution glycine to cysteine. Mutation 2 is a C to T transversion at nucleotide position 2227 (codon 717) with an amino acid substitution arginine to cysteine [6].

Incorrect diagnosis of CADASIL can lead to inappropriate treatments. For example, multiple sclerosis is treated with steroids and interferon beta-1a [8]. Stroke is treated with antiplatelet therapy. Currently there are no treatments for CADASIL [1]. Correct diagnosis therefore will avoid exposure to inappropriate drugs.

StrokeDX diagnosis of this genetic stroke syndrome can help clinical professionals corrected differentiate CADASIL from stroke or from multiple sclerosis. The clinical components of the CADASIL rule do not require DNA analysis nor biopsy data. The history and MRI images are sufficient to strongly suggest the diagnosis. Addition of software components to support the CADASIL diagnosis were completed in a few hours. This indicates that the StrokeDx framework (benchmark definition and rule declarations) is robust and easily extended.

Future work regarding CADASIL will included computing confidence factors that represent the extent of subcortical infarcts, confidence factors that represent the number of family members with stroke/migraine/dementia, and confidence factors that represent the extent of white matter disease in the temporal lobes. For example, the volume of white matter disease could map to confidence factor with high volume represented as a higher CF for that specific rule. Independent testing of StrokeDx by stroke experts is planned. This system can be used in the clinical setting or for training of medical practitioners.

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