

Syndrome of the month

X linked hydrocephalus and MASA syndrome

Sue Kenwrick, Monique Jouet, Dian Donnai

Abstract

X linked hydrocephalus and MASA syndrome are clinically related, neurological disorders with an X linked recessive mode of inheritance. Although originally described as distinct entities, their similarity has become apparent as the number of reported families has increased and a high degree of intra- and interfamilial variation in clinical signs noted for both disorders. Consideration of this clinical overlap together with finding that genes for both diseases map to the same chromosomal band (Xq28) led to the hypothesis that they were caused by mutation at the same locus. This was confirmed by identification of mutations in patients with X linked hydrocephalus and MASA syndrome within the gene for neural cell adhesion molecule L1. Here we review the clinical and genetic characteristics of these disorders and the underlying molecular defects in the L1 gene.

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Key words: hydrocephalus; X linked; MASA syndrome.

X linked hydrocephalus

HISTORY

X linked recessive hydrocephalus is the most common form of hereditary hydrocephalus (McKusick No 30700), with an incidence of approximately 1 in 30 000, and accounting for between 2% and 15% of primary idiopathic hydrocephalus in newborn males.^{1,2} It was first described in detail in a single large family by Bickers and Adams in 1949³ and rediscovered as a sex linked syndrome by Edwards in 1961.¹⁴ Since then, over 35 families have been reported and the existence of an X linked recessive form of hydrocephalus is well established.⁵⁻¹⁵

CLINICAL FEATURES

X linked hydrocephalus is associated with a wide variation in severity and spectrum of clinical signs and symptoms both within and between families. Onset of hydrocephalus often occurs in utero although its appearance may be too late for detection during routine ultrasound scanning even at 20 weeks' gestation.^{10,13,14,16} Accumulation of cerebrospinal fluid (CSF) is associated mainly with the lateral and third cerebral ventricles and often results in stillbirth

or early mortality. The degree and progression of hydrocephalus in these families is highly variable with some males not presenting with symptoms of increased intracranial pressure or macrocephaly despite enlargement of ventricles.^{2,10,17} In general, prominent ventricular dilatation and progressive hydrocephalus is associated with early mortality, whereas mild enlargement and arrest is consistent with long survival.

Valve insertion is an effective treatment for relieving high pressure hydrocephalus and improving life expectancy; however, survivors are always late in meeting their developmental milestones. They are mentally retarded with highly variable IQs ranging from "too low to test" to over 70¹⁸⁻²⁰ and exhibit variable degrees of spasticity with increased tone and hyperreflexia, particularly in the lower limbs. Reflexes and tone may be normal in the arms in the presence of marked lower limb spasticity.¹ These observations contrast with those described for non-X linked hydrocephalus where the majority of surviving cases have normal intelligence and little motor impairment.²

Flexion-adduction deformities of the thumbs (clapsed or adducted thumbs) are frequently but not always observed (Halliday *et al*² reported clapsed thumbs in 44% of cases) and may be associated with agenesis or hypoplasia of the abductor or extensor muscles of the thumb.^{21,22} The existence of affected subjects without obviously abnormal thumbs, and the presence of this feature in other syndromes^{23,24} means that this cannot be relied upon as a diagnostic sign.

A wide variety of brain malformations has been reported in association with X linked hydrocephalus including agenesis of the corpus callosum or septum pellucidum, fusion of the thalamic fornices, colliculi and corpora quadrigemina, and absence or hypoplasia of the corticospinal tract (CST), as assessed by histological analysis of the pyramids in cross sections of the medulla.^{4,8,25-28} The latter observation provides an explanation for the observed spasticity in this disease as increased tone with hyperreflexia are characteristic signs of CST damage. The value of bilateral absence of pyramids (BAOP) as an indicator of X linked hydrocephalus was investigated by Chow²⁵ and Halliday *et al*.² They determined that an association exists between BAOP and X linked hydrocephalus although the sample size was small. Nine out of nine patients with clear or

University of
Cambridge
Department of
Medicine, Level 5,
Addenbrooke's
Hospital, Hills Road,
Cambridge CB2 2QQ,
UK
S Kenwrick
M Jouet

Department of
Clinical Genetics,
St Mary's Hospital,
Whitworth Park,
Manchester M13 0JH,
UK
D Donnai

Correspondence to:
Dr Kenwrick.

“probable” (by clinical criteria) X linked disease were found to have absent pyramids whereas six out of six control male cases of congenital hydrocephalus were not. BAOP is not restricted to cases of X linked hydrocephalus and can be found in other congenital conditions, such as holoprosencephaly and hydranencephaly. Nevertheless, the uncommon nature of BAOP means that it deserves special attention when assessing isolated cases of hydrocephalus for the possibility of the hereditary disorder.

Stenosis of the aqueduct of Sylvius was originally thought to be the primary cause of hydrocephalus as it was observed in several of the first patients characterised in detail.³⁴ The acronym HSAS (for hydrocephalus owing to stenosis of the aqueduct of Sylvius) was therefore adopted. Although the aqueduct has been found to be patent in several subsequent examples,^{5 14 22} accurate measurements have rarely been obtained. Although a degree of aqueductal stenosis may well contribute to X linked hydrocephalus it cannot be considered diagnostic for the hereditary condition as it is found in up to 40% of patients with hydrocephalus.²⁹

A variety of ocular, musculoskeletal, and neurological abnormalities have also been reported in cases of X linked hydrocephalus including nystagmus, ptosis, optic atrophy, scoliosis, torticollis, lumbar lordosis, and seizures. There are no consistent distinguishing facial characteristics although prominent ears have been reported.^{1 18}

Thus, X linked hydrocephalus is associated with an extremely wide variation in severity and clinical signs. Overall the most consistent features are hydrocephalus, mental retardation, and lower limb spasticity consistent with upper motor neurone damage (fig 1).

MASA syndrome

HISTORY

The term MASA syndrome (McKusick 303350), an acronym for Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs, was coined by Bianchine and Lewis³⁰ in 1974 to describe the tetrad of X linked clinical signs observed in a single large Mexican family. Since then several reports have detailed similar families, although they have been described variously as spastic paraplegia type I (SPG1, McKusick 312900) or clasped thumb-mental retardation syndrome, as well as MASA syndrome. Again there is a high degree of inter- and intrafamilial variation in clinical presentation.³⁰⁻⁴⁰

CLINICAL FEATURES

The clinical profiles described for MASA syndrome patients clearly overlap with those observed for X linked hydrocephalus, although the lack of congenital high pressure hydrocephalus results in a longer life expectancy. Mental retardation, lower limb spasticity, and hyperreflexia are observed in all cases although the degree of impairment can be mild. Flexion-adduction deformities of the thumbs are found in most, but not all cases and there is a general

deficit in development of expressive relative to receptive language. Additional clinical signs include optic atrophy, lordosis, scoliosis, torticollis, cleft palate, seizures, inguinal hernia, and urinary tract abnormalities. Although MASA is not defined as including hydrocephalus, imaging in a limited number of patients has shown enlargement of cerebral ventricles^{6 38} and a variety of other brain malformations including agenesis of the corpus callosum.

The early suspicion that X linked hydrocephalus and MASA syndrome are caused by the same X linked locus^{38 39} was reinforced by the observation that both are the result of genes in the same subchromosomal band (see below) and reports of single families with both MASA and congenital hydrocephalus cases.^{38 41}

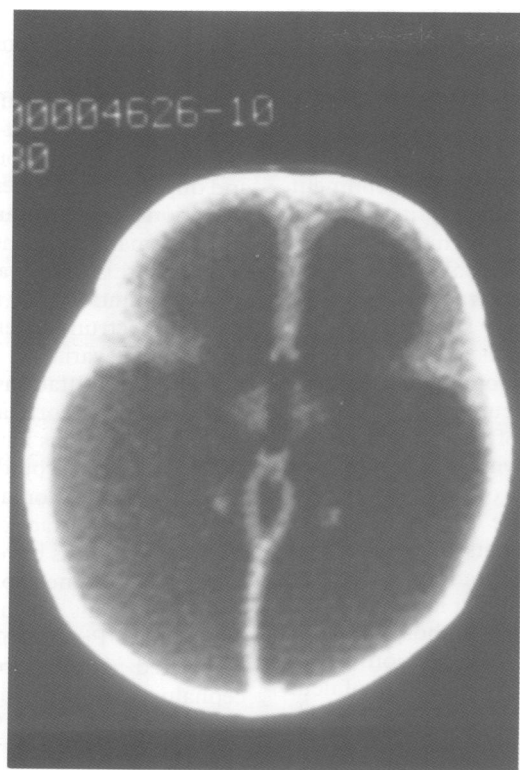
Genetics

X linked hydrocephalus and MASA syndrome behave as classical X linked recessive disorders with very few carrier females showing signs of disease. Preferential inactivation of one X in lymphocytes has been shown in manifesting carriers of one family suggesting that non-random X inactivation is responsible for the phenotype in females.³⁴

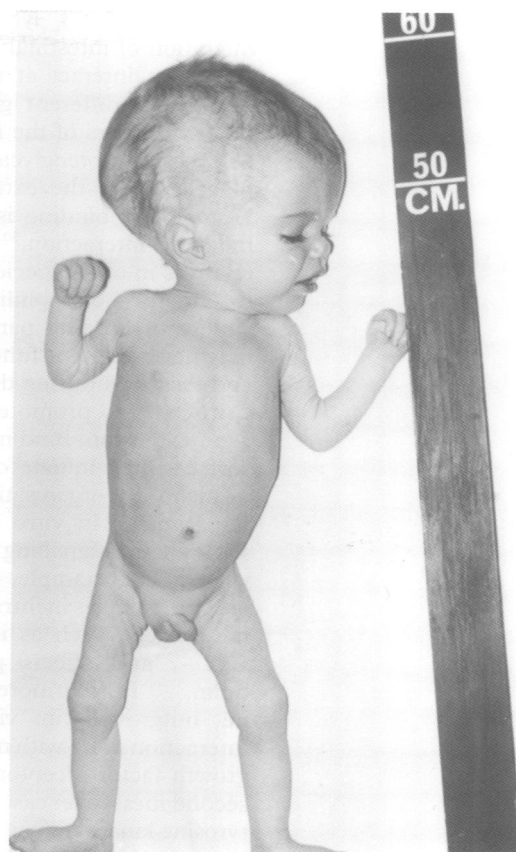
The search for a single gene responsible for X linked hydrocephalus and MASA syndrome began in earnest when genetic linkage analysis provided evidence for loci for both syndromes in subchromosomal band Xq28 with little indication of genetic heterogeneity.^{13 35-37 39 42} Further pedigree analysis allowed refinement of the relevant interval to approximately 1.5 megabases of genomic DNA between polymorphic markers DXS52 and DXS605,^{7 11 15 38} a region containing the gene for neural cell adhesion molecule L1.⁴³ Assessment of this gene in X linked hydrocephalus and MASA syndrome families provided the final proof that the two disorders are indeed caused by mutation at a single locus in Xq28.

Neural cell adhesion molecule L1

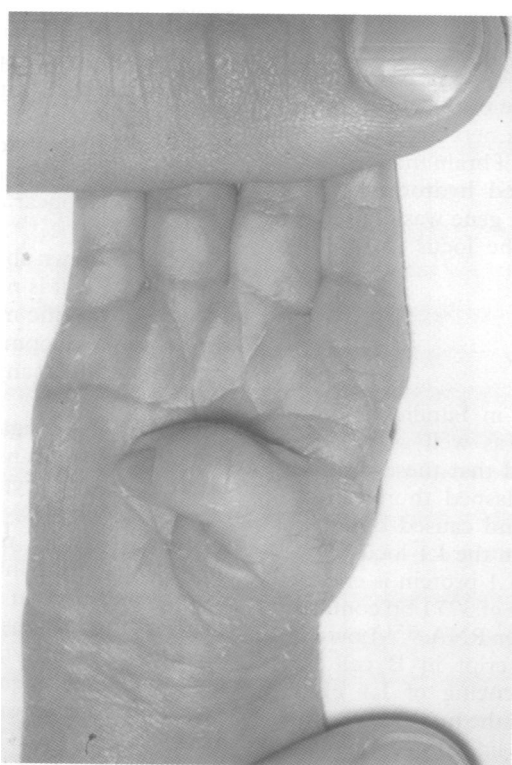
Neural cell adhesion molecule L1 is a multi-domain, highly conserved cell surface glycoprotein expressed primarily on the axons of developing neurones. It is a member of the immunoglobulin superfamily consisting of six domains with core structural motifs similar to those found in immunoglobulins (Ig type C2), five domains similar to type III repeats found in the extracellular matrix protein fibronectin (Fn type III), a short transmembrane region, and a cytoplasmic region. Results of in vitro assays and antibody perturbation experiments indicate that L1 is involved in neuronal migration and neurite (for example, axon) extension as well as fasciculation.⁴⁴⁻⁴⁶ During development L1 is located on subsets of migrating neurones, at the surface of long axons, and on growth cones and it continues to be expressed in the adult nervous system on unmyelinated axons. Although mainly neuronal, expression at other sites suggests that it may also play a part in myelination of peripheral



(A)



(B)



(C)



(D)

Figure 1 Examples of clinical signs in patients with X linked hydrocephalus or MASA syndrome. For all subjects mutations within the *L1* gene have been detected. (A) Axial CT scan of a neonate from an X linked hydrocephalus family showing gross lateral and third ventricle dilatation and extreme thinning of the cortical mantle. Appearances are compatible with aqueductal stenosis. (B) An infant with X linked hydrocephalus: note the enlarged head and clasped thumbs. (C) A view of an adducted right thumb in the infant shown in (B). (D) Spastic lower limbs in a subject described as having MASA syndrome.

nerves, B and T lymphocyte function, and migration of intestinal crypt cells.⁴⁷⁻⁴⁹

L1 can interact at the cell surface with a number of different glycoproteins, including other members of the immunoglobulin superfamily, and proteoglycans either on the surface of cells or in the extracellular environment. Homophilic binding is probably its principle mode of interaction,⁵⁰ although L1 (or close relatives in other species) has also been shown to undergo heterophilic interactions.⁵¹⁻⁵⁶ This variety of binding partners suggests that L1 may have different functions at different times and locations during development.

In order to promote neuronal migration or axon extension, binding of L1 at the neuronal surface must initiate downstream events that result in a reorganisation of the cytoskeleton. Experiments *in vitro* have begun to unravel some of the signalling events that may be involved. For example, L1 homophilic binding induces changes in intracellular levels of second messengers, such as inositol phosphates and Ca²⁺, and affects phosphorylation of tubulin.⁵⁷⁻⁶⁰ Furthermore, L1 promotion of neurite outgrowth *in vitro* may involve cis-interaction of L1 with members of the fibroblast growth factor receptor family which initiate a second messenger cascade via their cytoplasmic tyrosine kinase domains.⁶¹ L1 may also directly interact with the cytoskeleton via binding of its cytoplasmic domain to ankyrin.⁶² The relevance of these interactions to L1 function *in vivo*, the purpose of different L1 ligands, and the role of individual domains of the protein have yet to be determined. In view of the role of L1 in the morphogenesis of the nervous system and the common occurrence of brain malformation in patients with X linked hydrocephalus or MASA syndrome, the L1 gene was considered a prime candidate for the locus involved in these disorders.

Mutation analysis

Detection of mutations in families suffering from MASA syndrome as well as X linked hydrocephalus confirmed that these disorders (including SPG1 and clasped thumb-mental retardation) are allelic and caused by heterogeneous mutations within the L1 locus.^{8,9,63-70}

The 143 kDa human L1 protein is encoded by an open reading frame of 3771 bp contained within a 4.5 kb messenger RNA.^{71,72} Low level expression of this transcript in B cell lines enabled complete sequencing of L1 cDNA from patients resulting in the first evidence that L1 corresponds to the X linked hydrocephalus locus.^{66,67} More flexibility in the approach to mutation searching has been provided by resolution of the genomic structure of the L1 gene and determination of sequences at intron-exon boundaries (A Rosenthal, EMBL database HSN CAMX). The gene consists of 28 exons distributed across 15 kb of genomic DNA and conditions have been established for amplification of each exon.⁹

To date, 25 different L1 mutations have been reported in as many families and these are

represented in fig 2. Virtually every form of mutation has been found with the notable exception of whole gene deletion. Missense mutations are the most common, representing over half of those reported (14), although splicing (5), frameshift (2), nonsense (2), deletion (1), and duplication (1) events have been described. Mutations are distributed across the L1 gene affecting many different domains of the protein. Although this wide variation in position and type of mutation may in part explain the wide clinical spectrum observed for these disorders, intrafamilial variation coupled with a lack of clustering of mutations confounds strict genotype/phenotype correlations.

Three mutations have been described (H23, H44, H24) that would truncate L1 before the transmembrane domain, eliminating the potential for cell surface expression of the protein. As no L1 isoforms have been described without a transmembrane domain, subjects bearing these mutations presumably lack L1 function completely. Predictably, these mutations are associated with severe congenital hydrocephalus and early mortality.^{8,9} By contrast, three mutations (H29, H13, MASA3) that truncate the protein in the cytoplasmic domain, allowing cell surface presentation, were found in families described as having MASA syndrome.

To date, five mutations described affect processing of L1 hnRNA. In all of these cases production of normal as well as aberrantly spliced mRNA is apparent from studies on cDNA from B cell lines. If these results can be extrapolated to the nervous system, they indicate that L1 splicing mutations act in a dominant negative fashion at the cellular level, although they appear recessive in heterozygous females.

As little is known about the roles of individual domains of L1, it is not possible to predict the outcome of specific mutations on L1 function and neural development. The distribution of mutations across many domains, however, suggests that they may affect interaction with a variety of different ligands (for the extracellular domain), signal transduction, as well as interactions with cytoskeletal proteins (intracellular domain). Some insight into the potential effects of mutations on L1 protein can be gained from interspecies sequence comparisons and protein modelling. For example, several of the missense mutations described to date affect residues that are highly conserved between like domains within L1 as well as between L1-like proteins in different species (for example, C264Y, G121S, R184Q, and G452R). That these mutations are likely to affect the structural integrity of individual domains is borne out by comparison with models of immunoglobulin domains related to those present in L1⁷³ (C Chothia, personal communication). Those affecting less conserved residues (for example, D598N, H210Q, and E309K) are more likely to affect ligand recognition or quaternary folding of the mature protein (for a comparison of residues affected by missense mutations see ref 8).

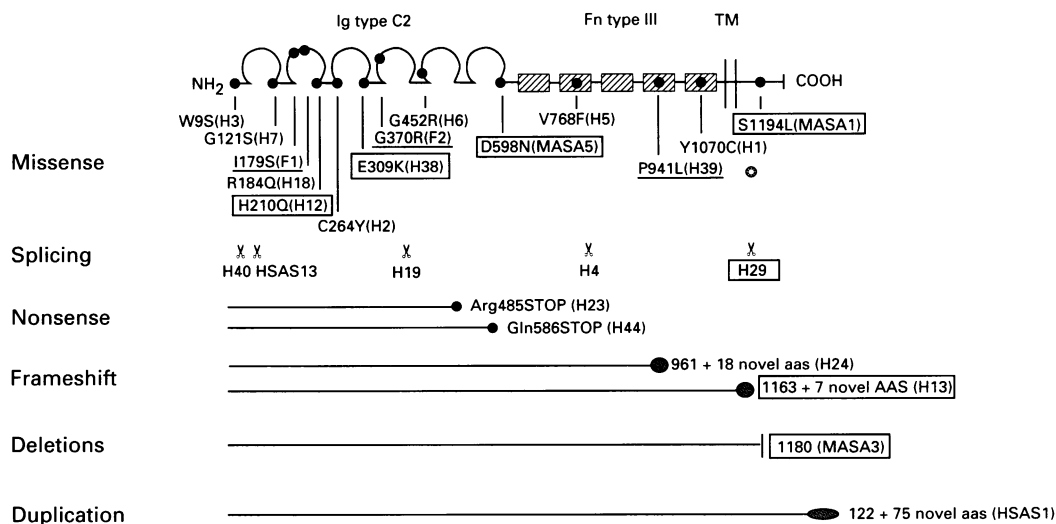


Figure 2 Published mutations in the *L1* gene in relation to *L1* protein structure. Protein domains: Ig type C2 (immunoglobulin-like domains), Fn type III (fibronectin type III domains), TM (transmembrane region). H, HSAS, MASA, and F numbers represent the names given to individual families by authors. Boxed family numbers indicate families described as MASA syndrome (or clasped thumb-mental retardation or SPG1). Underlined numbers highlight families with examples of HSAS as well as MASA syndrome (or SPG1). For all mutations numbering of residues within *L1* uses the first methionine as amino acid number 1. Missense mutations are given using the single letter amino acid code. Positions affected by splicing mutations are indicated by scissors. For all other mutations the solid line represents intact *L1* protein up to the point affected by mutation. For deletion MASA 3 the C-terminal 77 residues of *L1* would be deleted and for a DNA duplication in HSAS1 the terminal 35 amino acids would be replaced by 75 new residues.

Several explanations can be put forward for the observed lack of whole gene deletion. Large deletions may incorporate additional genes whose function is essential for viability or whose absence would give rise to a different phenotype. In this regard it is interesting that the chromosomal region surrounding *L1* is rich in expressed sequences.⁷⁴ This may be coupled with a lack of sequences predisposing to deletion in the immediate vicinity of the *L1* gene and the relatively small size of genomic *L1*. Alternatively, complete deletion of *L1* itself may be lethal or give rise to a phenotype not recognisable as X linked hydrocephalus or MASA syndrome.

Pathology in relation to *L1* function

Identification of the *L1* gene as a disease locus provides an opportunity for examining its function in human development. Despite the fact that *L1* expression is found throughout the nervous system and is implicated in neuronal migration and neurite extension, CNS and PNS architecture is grossly preserved even in cases where the gene mutation would eliminate cell surface expression of *L1*. Normal lamination of the cortices of the cerebrum and cerebellum, for example, is maintained.^{3 27 28} This is not unexpected as *L1* is one component of a highly complex network of interacting, and often related, cell adhesion molecules some of which may have overlapping functions. Perhaps the most dramatic distinguishable morphological sign in cases of X linked hydrocephalus is hypoplasia of the corticospinal tract (CST). That this is not secondary to raised intracranial pressure is implied by the fact that CST absence is not a general feature of congenital hydrocephalus.² A prominent role for *L1* in the development of this tract of neurones

is consistent with the high levels of expression observed during rat CST genesis.⁷⁵

In summary, neuropathological investigations in patients with *L1* mutations indicate that the protein must have a prominent role in the development of the corticospinal tract, which is consistent with the spasticity observed in patients. No explanation can be provided at present for other features such as mental retardation, adducted thumbs, or ventricular dilatation. Furthermore, the precise function of *L1* in some areas of high expression, such as the cerebellum, is not illuminated by existing neuropathology.

Diagnosis

From a clinical point of view identification of the gene for this group of disorders enables accurate diagnosis and early detection in utero.⁶⁵ This is particularly relevant for small pedigrees or families with isolated cases. A priori the recurrence risk for male sibs of a hydrocephalic boy is 4%,^{2 76} which rises to 50% where the X linked disease is identified. The problem is therefore one of having to recognise the small proportion of hydrocephalic males with a mutation in *L1* when X linked inheritance is not apparent. Unfortunately, routine mutation screening of all hydrocephalic boys is impractical (primary idiopathic hydrocephalus occurs in about 0.6 per 1000 live births²) and no absolutely reliable method of diagnosing X linked hydrocephalus in sporadic cases has yet been developed. However, where survival is long enough for additional signs, such as spasticity, mental retardation, and flexion deformities of the thumbs, to be observed, screening for an *L1* mutation should be considered.⁶⁵ Where possible, suitable imaging should be used to assess pyramidal tract status

in view of the association of BAOP with X linked disease. The wide variation in clinical signs observed in subjects with a proven L1 mutation means that inevitably sporadic cases will be hard to diagnose and some will escape attention.

For families with a clear X linked pattern of inheritance of hydrocephalus or MASA syndrome there is very little indication of heterogeneity. There are only two published examples of families with a disorder that recombines with an Xq28 haplotype^{15,77} and an L1 mutation that segregates completely with hydrocephalus has been identified for one of these families (M Jouet, unpublished data).

Conclusions

In summary, X linked hydrocephalus and MASA syndrome represent a clinical spectrum owing to a heterogeneous group of mutations in the gene for neural cell adhesion molecule L1. These naturally occurring mutations serve to highlight regions of L1 that must be critical for correct function of the protein. Therefore, continued mutation analysis in these disorders combined with thorough neuropathology and assessment of the functional consequences of mutation promises to provide valuable insight into the function of this cell adhesion molecule during human development as well as provide tools for accurate diagnosis.

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