Neuroimaging findings in MOGAD – MRI and OCT

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Abstract

Summary Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are rare in both children and adults, and have been recently suggested to be an autoimmune neuroinflammatory group of disorders that are different from aquaporin-4 autoantibody associated neuromyelitis optica spectrum disorder and from classic multiple sclerosis. In vivo imaging of the MOGAD patient central nervous system has shown some distinguishing features when evaluating magnetic resonance imaging of the brain, spinal cord, optic nerves, as well as retinal imaging using optical coherence tomography. In this review, we discuss key clinical and imaging characteristics of paediatric and adult MOGAD. We describe how these imaging techniques may be used to study this group of disorders and discuss how these imaging methods have led to recent insights for consideration in future studies.

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Summary

Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are rare in both children and adults, and have been recently suggested to be an autoimmune neuroinflammatory group of disorders that are different from aquaporin-4 autoantibody associated neuromyelitis optica spectrum disorder and from classic multiple sclerosis. In vivo imaging of the MOGAD patient central nervous system has shown some distinguishing features when evaluating magnetic resonance imaging of the brain, spinal cord, optic nerves, as well as retinal imaging using optical coherence tomography. In this review, we discuss key clinical and imaging characteristics of paediatric and adult MOGAD. We describe how these imaging techniques may be used to study this group of disorders and discuss how these imaging methods have led to recent insights for consideration in future studies.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) IgG antibody associated disorders (MOGAD) describe a new entity of demyelinating neurological syndromes defined by the presence of serum IgG autoantibodies against MOG detected by cell-based assays (1–3). MOGAD occur in both children and adults and comprise a heterogeneous disease spectrum (4,5). Clinical presentation can include monophasic or recurrent episodes of optic neuritis (ON), myelitis, brainstem syndromes, acute disseminated encephalomyelitis (ADEM), and symptoms of encephalitis such as seizures (6,7). Overall, MOGAD are rare with an incidence of around 1.1 - 2.4 per million people (8) and are more frequent in children compared with adults, as shown in a recent Dutch cohort with an incidence of 3.1 per million in children (9).

Importantly, a direct pathophysiological effect of the MOG-IgG in the central nervous system has yet to be elucidated (2). Therefore, it remains unclear whether MOG-IgG has a direct pathogenic role or whether it is rather a biomarker, that is a possible reflection of an immunological response from disrupted myelin in the MOG-IgG associated demyelinating disease spectrum. However, increasing clinical and pathological evidence now strongly indicates that MOGAD represent a distinct disease entity different from other neuroinflammatory and demyelinating diseases, such as multiple sclerosis (MS) or aquaporin-4 (AQP4) IgG positive neuromyelitis optica spectrum disorder (NMOSD) (10–15). Moreover, these conditions apparently exhibit differential responses to immunotherapies, underscoring the necessity for accurate and timely diagnostic procedures during which neuroimaging play a paramount role (16–21). Due to the widespread nervous system affection in MOGAD, magnetic resonance imaging (MRI) and optical coherence tomography (OCT) are important imaging tools in gaining more knowledge about the disease and for the monitoring of patients with this rare set of disorders (22,23). This review article will give an overview of the clinical, radiological, and advanced imaging aspects which are currently of high interest in the MOGAD clinical research community.

MOGAD clinical presentations

The clinical phenotype of MOGAD is broad and includes uni- and bilateral anterior ON, long and short transverse myelitis (TM), ADEM, brainstem encephalitis, and cortical encephalitis with or without seizures (2). In addition, combinations of these syndromes are common, e.g. as NMOSD-like phenotype presenting with ON and TM (12). Importantly, the clinical phenotype strongly depends on age; with a more ADEM-like phenotype in children and a more optico-spinal phenotype in adolescents and adults (2). In paediatric patients, the following four phenotypes account for 90% of MOGAD cases: 46% presenting with ADEM, 30% with ON, 11% with TM, and 4% with a NMOSD-like phenotype (ON+TM) (24). Relapses in both children and adults are common, occurring in around 40-80% of patients, especially in the form of ON (6,25–27).

Acute disseminated encephalomyelitis (ADEM)

MOG-IgG serum antibodies were first identified in a subset of children with ADEM (28,29). Children with ADEM represent the most common phenotype among all MOGAD patients and account for almost 50% of paediatric MOGAD patients (2,24). Clinical presentation of ADEM includes polyfocal neurological deficits and encephalopathy (i.e. behavioural changes or altered consciousness), not explainable by fever (30). It has recently been shown that up to 50% of all children with ADEM are seropositive for MOG-IgG (31). In these patients, MOG-IgG seroprevalence is associated with a higher risk for longitudinally extensive transverse myelitis (LETM), but with resolution of brain lesions and a better outcome compared to MOG-IgG negative ADEM patients (32). Relapses can occur with further episode(s) of ADEM as multiphasic ADEM (MDEM), with ON (ADEM-ON), or transverse myelitis (ADEM-TM) (33). Notably, persistent seroprevalence of MOG-IgG is strongly associated with an increased risk for relapsing disease (34,35).

Optic neuritis (ON)

ON is the most common clinical presentation of MOGAD in adults, comprising around 50% of MOGAD phenotypes at onset, as shown by three large national studies from the UK, France, and Sri Lanka (6,25,36). Clinical symptoms of ON include blurred vision and reduced visual acuity or visual loss, as well as eye pain especially retrobulbar pain with eye movement (37). ON in MOGAD is often bilateral, either concurrently or sequentially (38,39). Therefore, bilateral ON represents an important clinical presentation that can help differentiate MOGAD-ON from ON in multiple sclerosis (MS-ON). However, incidence of bilateral ON in paediatric patients is similarly common in AQP4-IgG positive NMOSD as it is in MOGAD patients. Differences include a more anterior affection of the optic nerve in MOGAD with optic nerve head swelling and retrobulbar involvement (40).

Myelitis

Myelitis is the second most common clinical presentation in adult MOGAD patients, accounting for around 20% of disease-related attacks, while it is less common in children (9,25,36). LETM, defined as a spinal cord lesion spanning three or more vertebral segments in length, is a common finding in MOGAD (41). Typical symptoms include motor and/or sensory deficits (numbness), bladder, bowel, and/or erectile dysfunction (41). Neuropathic pain has been implicated in NMOSD to be related to the level(s) at which spinal cord lesion(s) are located, which could be the case in MOGAD patients as well, since the 86% of MOGAD patients in one study reportedly suffered from chronic pain (42–45). Clinical differences distinguishing myelitis in MOGAD vs. MS or AQP4-NMOSD are: a higher percentage of patients are male, frequency of bladder and erectile dysfunction, younger age, prodromal infection and concurrent ADEM. However, short myelitis can also occur and is found in up to 38% of MOGAD cases (46,47). Unsurprisingly, bladder dysfunction has been found to be more prevalent in MOGAD patients with LETM compared to those with short myelitis (47).

Neuromyelitis optica spectrum disorder (NMOSD)

A combination of ON and/or myelitis is a common clinical phenotype of NMOSD. Neuromyelitis optica (NMO) was traditionally characterised by recurrent uni- or bilateral ON and TM, and was later expanded to a broader spectrum with restricted or extended forms including brainstem syndromes, referred to NMOSD (12,48,49). Around one-third of AQP4-IgG negative NMOSD patients harbour IgG serum autoantibodies against MOG (12,50). NMOSD as the presenting phenotype in MOGAD occurs in 5-20% of patients (6,25,51). Therefore, in patients with an optico-spinal phenotype, MOGAD represents an important differential diagnosis to AQP4-NMOSD, especially since the combination of myelitis with ON seems to be more common in MOGAD compared to AQP4-NMOSD (12,51,52). Similar to AQP4-NMOSD, MOGAD can also present with brainstem symptoms including intractable nausea, vomiting and hiccups, described as area postrema syndrome (53). However, the area postrema syndrome is less common in MOGAD (54).

Encephalitis

Epileptic seizures were repeatedly described in a subgroup of MOGAD patients and are more common than in AQP4-IgG seropositive NMOSD (55–57), occurring in around 20% of all adult and paediatric MOGAD patients (58).

Encephalitis with and without seizures is now becoming increasingly recognised as an important clinical phenotype of MOGAD (58). Here, patients can show neuropsychiatric symptoms, behavioural changes, seizures, and memory or speech problems (59). Recently, encephalitis with MOG-IgG has been described as the most common type of autoimmune encephalitis in children (60).

Other rare types of clinical presentation

Another rare presentation of MOGAD is found in children that show similar symptoms of ADEM, however, with a more progressive disease course (61). Here clinical course and symmetrical confluent cerebral MRI changes resemble that of children with leukodystrophy, hence the term leukodystrophy-like phenotype. Recently, overlapping central and peripheral nervous system syndromes have been described as potential additional MOGAD phenotypes, including cranial nerve involvement, myeloradiculitis, inflammatory neuropathies and combined central and peripheral demyelination syndromes (62–66).

MRI in MOGAD

MRI abnormalities in MOGAD can be detected in the brain, the optic nerve, and/or the spinal cord, and often depending on the clinically affected anatomical region of the nervous system. On cerebral MRI, findings in children most commonly reflect signs of ADEM with diffuse, widespread white matter T2-lesions, while in adults brainstem or cortical lesions are more common (2). Acute ON can lead to swelling of the optic nerve and to severe retinal neurodegeneration over time (67–70). Typical MRI findings of ON in MOGAD are long lesions in the anterior part of the optic nerve with periorbital enhancement and often bilateral affection (40). Spinal cord lesions in MOGAD can be visualised using MRI typically showing LETM affecting mainly the grey matter as seen as an "H-sign" on axial plane (41). Important differential disease diagnoses via MRI findings in MOGAD include its distinction from MS and AQP4-IgG seropositive NMOSD (71,72). The following sections describe common radiological presentations found in MOGAD, as well as advanced MRI techniques with the potential to further evaluate central nervous system changes in these disorders.

Radiological Presentation on Clinically Routine MRI

Cerebral MRI

Cerebral MRI changes in MOGAD are highly dependent on age. In children, typical MRI findings of ADEM are found in 40-50% of MOGAD cases (7). These include widespread supra- and infratentorial, asymmetrical diffuse white matter T2-hyperintensive lesions (32,73). Additional bilateral thalamic lesions were more common in MOG-IgG positive compared to MOG-IgG negative ADEM paediatric patients (74). In adults, brain MRI lesions are typically few and often either found infratentorially or presenting as cortical lesions (75,76), however there have been observations of large, confluent T2-hyperintense lesions in the white matter similar to ADEM (11).

Brainstem lesions can be found in up to 30% of adult MOGAD patients (6,77). These lesions are typically poorly demarcated, often located in the pons, around the 4^{th} ventricle, or the cerebellar peduncles and show resolution over time (75). Importantly, isolated brain or brainstem lesions are rare in adults and more often occur in combination with optico-spinal lesions (6). One patient presented with an initial MRI pattern typical of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and then subsequently developed LETM leading to a diagnosis of MOGAD (78).

Isolated T2-hyperintense cortical lesions visible on fluid-attenuated inversion recovery (FLAIR) sequences in both adult and paediatric patients with seizures were identified and referred to as FLAMES: FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (76,79). In these patients, cerebral MRI demonstrates unilateral or bilateral cortical T2-hyperintense lesions, but can also include deep grey matter, white matter, and brainstem lesions (55,57,80). In paediatric MOG-associated autoimmune encephalitis, cerebral MRI findings include extensive cortical and/or subcortical grey matter involvement without the typical white matter lesions seen in ADEM (4,60). Importantly, cerebral MRI in these children was normal in only 9% of the cohort, which is much less compared to other types of autoimmune encephalitis, such as anti-NMDA-receptor encephalitis where MRI can be normal in around 50% of the patients (81). In young

children presenting with the rare leukodystrophy-like MOGAD phenotype, cerebral MRI shows extensive confluent symmetrical white matter lesions with progression over time (61).

Since MOGAD represents an important differential diagnosis from MS and AQP4-NMOSD using radiological features, several studies assessed potential differences on MRI. A distinct pattern of MRI lesions defined by the so-called Matthews-Jurynczyk criteria can help differentiating MOG-NMOSD vs. MS strongly favouring MS over MOGAD, when: i) [?] 1 lesion adjacent to a lateral ventricle and in the inferior temporal lobe, ii) subcortical U-fibre lesions, and iii) Dawson's finger-type lesions (75,82,83). However, these studies did not report criteria to help discriminate between MOGAD and AQP4-NMOSD patients (84). The brainstem is a location where both MOGAD and AQP4-NMOSD patients can present with lesions (75,83), while cortical and juxtacortical lesions are more frequently found in MOGAD versus AQP4-NMOSD patients. Moreover, the area postrema syndrome that often affects AQP4-NMOSD patients with its corresponding MRI lesions, is not a characteristic feature in MOGAD (54).

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Figure 1. Cerebral MRI in paediatric MOGAD.

A) & B) Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI sequences of a 3-year-old female MOG-IgG positive acute disseminated encephalomyelitis (ADEM) patient showing bilateral white matter and deep grey matter thalamic lesions. C) Axial T2-weighted MRI sequence of a 12-year-old female patient with MOG-IgG positive ADEM and bilateral optic neuritis (ON) showing optic nerve swelling and hyperintensity.

Optic nerve MRI

MRI findings in ON can include T2-hyperintense lesions, nerve swelling, and gadolinium enhancement of the affected optic nerve on T1-weighted imaging. In MOG-ON, optic nerve lesions are frequently extensive, also termed longitudinally extensive ON (LEON), affecting more than half of the pre-chiasmatic optic nerve length (40,85,86). Moreover, MOG-ON predominantly affects the anterior part of the optic nerve. This can help with differentiating MOG-ON from AQP4-ON, which is also often extensive, but predominantly affecting the posterior part of the optic pathway (including the optic chiasm) (40,87–89). In contrast, MS-ON typically involve shorter segments of the optic nerve compared to both MOG-ON and AQP4-ON. Meanwhile, bilateral ON is specifically more frequent in MOG-ON than in MS-ON, and in paediatric patients have been associated with higher MOG-IgG titers (38,40). Another characteristic feature described in MOG-ON is perineural or periorbital gadolinium enhancement in the orbital soft-tissue that is not typically found in MS-ON (51,85,86,90–92).

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Figure 2. Spinal cord MRI in paediatric MOGAD.

Sagittal (A) and transversal (B) T2-weighted spinal cord MRI of a 12 year-old female patient with MOG-IgG positive ADEM. B) LETM with grey matter spinal cord affection presenting with the "H-sign", and A) as longitudinal hyperintense line. C) Sagittal T2-weighted cervical cord MRI in a 3-year-old female patient with MOG-IgG seropositive ADEM (same patient as shown in Figure 1A-B).

Spinal cord MRI

Typical spinal cord MRI changes in both children and adult MOGAD patients are TM, often in the form of LETM, but also as short myelitis (46). MOGAD patients commonly present with LETM affecting the cervical and/or thoracic cord (41,47,51,73). LETM is also a main radiological feature in AQP4-NMOSD

(46). Compared to AQP4-TM, conus involvement and multiple spinal cord lesions have been more frequently observed in MOG-TM (41,93,94). Short myelitis, which is typical of MS, can similarly be found in MOG-TM, however it is not found often in AQP4-TM (27,41,47,95,96). MOG-TM may present in spinal cord MRI as a hyperintense "H-sign" observed in the axial orientation, while imaged as a longitudinal thin vertical line in the T2-weighted sagittal plane image. This suggests a predominant affection of the spinal cord grey matter, as opposed to AQP4-TM, which may not be as centrally located in the cord (41,97,98). Gadolinium contrast-enhancement of spinal cord lesions is less common in MOG-TM compared to lesions in MS or AQP4-TM (41). Importantly, spinal cord MRI can initially be normal in MOGAD, although rare (99).

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Figure 3. Adult MOGAD patient cerebral and spinal cord affection.

A) T2-weighted FLAIR MRI sequence in the axial orientation showing large, confluent hyperintense lesions in the white matter. B) In the coronal view of the same cerebral scan as in A), it can be seen that the lesions extend toward the cortex. C) T2-weighted spinal cord MRI shows short segment lesions, seeming to be located centrally in the cord.

Advanced MRI techniques

Advanced MRI techniques include brain and spinal cord volumetric analyses, diffusion tensor imaging (DTI), and resting-state functional MRI. These techniques are usually not applied as part of the clinical routine workup in MOGAD patients, and quantitative volumetric and/or microstructural grey and white matter analyses using advanced MRI techniques are few. Recent studies, however, have identified specific changes in MOGAD patients that are potential new imaging biomarkers and tools for a better understanding of MOGAD disease pathology (23,100–102).

Although brain lesion distributions have been found to differ between MOGAD and AQP4-NMOSD patients, brain MRI volumetry did not show any differences in MOGAD patients compared to healthy controls in whole brain, deep grey matter, or white matter volumes (100,103). In children with ADEM, reduced brain volume and failure of age-expected brain growth was found for both MOG-IgG seropositive and -seronegative patients (Bartels et al. submitted), similar to findings in paediatric anti-NMDA-receptor encephalitis and paediatric-onset MS (7,81,104).

Spinal cord MRI analysis could identify spinal cord atrophy in patients with MOGAD as compared to healthy subjects, which was found to associate with increased counts of historical myelitis attacks. However, cord lesion frequency and atrophy was found to be less frequent compared to AQP4-TM (41,101). In MOG-myelitis patients, another study showed that the grey matter volume in the spinal cord was reduced during the acute phase of the attack (102).

Resting-state functional MRI connectivity allows for the study of functional connectivity alterations, such as in the visual or sensorimotor networks of the brain (105–107). Recently, it was found that altered interhemispheric function in patients with MOG-ON can be observed compared to healthy controls using resting-state functional MRI (108).

Meanwhile, evaluating network and CNS changes using graph theory and network statistical methods for elucidating clinical attack-related damage in NMOSD patients has also shown promise. Both cortical topological network changes and deep grey matter volume changes have been detected in AQP4-NMOSD patients following ON attacks and in patients with a simultaneous combination of clinical attacks (109,110). These findings suggest there may be non-localised damage or affection in NMOSD, which could also be the case in MOGAD.

Using DTI, one study found decreased white matter integrity in adult MOGAD patients compared to healthy controls, specifically reduced parallel diffusivity within whole-brain white matter tracts (100). As demyeli-

nation represents a pathological hallmark in MOGAD, in-vivo imaging of myelin integrity could represent a promising technique to further identify disease mechanisms and disease courses in MOGAD (111). Further studies applying more advanced sequences representative of myelin, such as T1-weighted/T2-weighted intensity-ratio, multi-parameter mapping, and magnetization transfer MRI analysis in MOGAD patients may help in identifying more subtle MRI changes in the future (112–114).

OCT in MOGAD

The quantitative and qualitative assessment of the retinal changes over time can be performed in close-to-cellular resolution using spectral domain optical coherence tomography (OCT) (23,115). Improvement of OCT techniques in the past decade has allowed the retina to be examined in greater detail. The unprecedented resolution of down to 3.9 µm enables measurement of retinal ganglion cell loss, evaluated by the combined macular ganglion cell layer and inner plexiform layers (mGCIPL) and their axons, as measured by the peripapillary retinal nerve fiber layer (pRNFL). These OCT metrics have been shown to correlate well with visual function and the damage that occurs in NMOSD and MS patients (116,117) Thus, OCT is a valuable tool for monitoring many neuro-ophthalmological and neurological conditions, including NMOSD and MOGAD (Figure 4) (68,118,119).

Acute ON in MOGAD is often bilateral and localised in the anterior optic nerve inducing severe and characteristic retinal edema (120). Initially covered by the edema, the neuroaxonal layers of the retina (pRNFL, mGCIPL) degenerate significantly in the following months (Figure 5) (23,69,115,120,121). These losses accumulate with each additional ON episode, which occur frequently in MOGAD (69,70). Therefore, although a single episode does not often lead to disastrous damage (122,123), the highly recurrent ON attacks accumulate with pRNFL and mGCIPL loss. This is comparable to patients with AQP4-IgG seropositive NMOSD, which is characterised by less frequent, but more damaging ON episodes (70). In comparison with MS, MOGAD patients are described as undergoing more severe retinal neurodegeneration after ON, however a final consensus on this topic has not been reached (115,122,124).

Further studies are warranted to investigate retinal neurodegeneration independent of ON in MOGAD. One study performed a first exploratory analysis in a small dataset recording pRNFL loss without associated GCIPL reduction (125). Apart from true retinal neurodegeneration, this could potentially be explained by a remission of attack-associated edema, which commonly affects the RNFL more than the ganglion cell layer (126). If the absence of ON-independent GCIPL loss is confirmed, this would not only stress the importance of ON attack-prevention in MOGAD but also allow a better separation from MS and AQP4-IgG seropositive NMOSD, which are both affected by ON-independent retinal neuroaxonal loss.

OCT data in paediatric MOGAD is scarce. The results in paediatric cohorts generally mirror those in adults with measurable post-ON swelling and associated reduction and thinning of the pRNFL (69,127). There are, however, conflicting reports concerning unilateral ON cases with subclinical involvement of the contralateral, clinically healthy eye, an area which would benefit from further research given the potential detrimental impact on the otherwise healthy eye (127,128).

In both paediatric and adult presentations, and notwithstanding the high relapse rates and severe neuroaxonal degeneration, high-contrast visual acuity is surprisingly preserved in MOGAD patients compared with AQP4-IgG seropositive NMOSD patients although both groups have comparable neuroaxonal loss (70,122,129–131). How visual acuity is preserved in MOGAD remains unclear, but data suggests an influence of a primary retinal astrocytopathy in AQP4-IgG seropositive NMOSD accumulating in additional retinal changes with functional consequences (*Giegengack et al. in preparation*) (132). Nevertheless, MOGAD patients with their high prevalence of ON attacks, are at risk of irreversible visual impairment when deprived of a timely diagnosis and immunosuppression therapy.

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Figure 4. Retinal anatomy and optical coherence tomography.

A) Anatomical representation of the human retina, and B) the human retina as imaged using OCT. These images have been kindly reproduced and modified under a Creative Common Licence from www.neurodial.de. Abbreviations: RNFL: retinal nerve fiber layer, GCL: ganglion cell layer, IPL: inner plexiform layer, GCIP: ganglion cell and inner plexiform layer, OCT: optical coherence tomography.

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Figure 5. Macular scans from OCT.

Macular scans of various retinas with corresponding thickness scale (0-150μm) with heat maps highlighting the thickness variations across the macular GCIP layer. A) Variations in the thickness across various pathologies in different patients. B) Right eye of the same MOGAD patient prior to ON, after 2 ONs and after 4 ONs. Thinner areas are depicted with cooler colours (purple/blue) and thicker areas depicted with warmer colours (red/yellow). Abbreviations: HC: healthy control, ON: optic neuritis, MOGAD: myelin-oligodendrocyte glycoprotein antibody disorders, MOGAD-NON: MOGAD with no history of ON; AQP-4-IgG: aquaporin-4 immunoglobulin G.

Concluding remarks

MOGAD pathophysiology, disease treatment, and monitoring are currently of high interest in the autoimmune neuroinflammatory diseases research community. So far, most known MRI and OCT characteristics in MOGAD are based on small monocentric studies that yielded some contradicting results, thus multi-centred and prospective studies are necessary to validate findings. Such multi-centred studies are beginning to shed light on this rare disease, such as the Collaborative OCT in NMOSD (CROCTINO) and the PArallel MRI in NMOSD (PAMRINO) studies (133).

In vivo imaging, using MRI and OCT, has given clinicians and researchers insights into the central nervous system affection of this rare disorder at an unprecedented rate. As new technologies and analysis methods continue to be developed, along with the increase in open-sharing and collaborative, prospective studies on the horizon; we believe both MRI and OCT will lead the way towards personalised prognostics and treatment in MOGAD.

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