Differential diagnosis of non-MS optic neuropathies

8th Istanbul MS Days 17-OCT-2023;15:30-15:50 axel petzold

Disclosures

Stichting MS Research NL NIHR UK, UCSF, Amsterdam UMC Novartis, Roche, Heidelberg Academy



The ICON 2022 story

THE LANCET Neurology

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Optic Neuropathies

Published: September 22, 2022

Executive Summary

Optic neuropathies can reflect a wide range of pathophysiologies, both acquired and inherited. This Series provides an update on the clinical, imaging, and laboratory findings that differentiate these disorders, allowing clinicians to focus their diagnostic studies and optimise treatments. Multimodality optic nerve imaging—including fundus photography, optical coherence tomography, and MRI—has greatly advanced the diagnosis and follow-up of patients with optic neuropathies. Also reviewed in this Series, new evidence shows that optic neuritis can frequently indicate autoimmune neurological disorders, including multiple sclerosis and the recently recognised disease categories of aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder and myelin-oligodendrocyte glycoprotor nantibody-associated disease. Early clinical recognition of optic neuritis is, therefore, important for prognosis and treatment. Also reviewed in the Series, a unifying feature in the pathophysiology of hereditary disorders of the optic nerve is mitochondrial dysfunction. Treatments are emerging for optic neuropathies, including immunotherapies and genetic therapies.



Imaging of the optic nerve: technological advances and future prospects

Valérie Biousse, Helen V Danesh-Meyer, Amit M Saindane, Cédric Lamirel, Nancy J Newman *The Lancet Neurology* Published: September 22, 2022 Full-Text HTML | PDF

Optic neuritis and autoimmune optic neuropathies: advances in diagnosis and treatment

Jeffrey L Bennett, Fiona Costello, John J Chen, Axel Petzold, Valérie Biousse, Nancy J Newman, Steven L Galetta *The Lancet Neurology* Published: September 22, 2022 Full-Text HTML PDF

Understanding the molecular basis and pathogenesis of hereditary optic neuropathies: towards improved diagnosis and management

Nancy J Newman, Patrick Yu-Wai-Man, Valérie Biousse, Valerio Carelli *The Lancet Neurology* Published: September 22, 2022

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Polated Content

POSITION PAPER Diagnosis and classification of optic neuritis

Axel Petzold, Clare L Fraser, Mathias Abeg Raed Alroughani, Daniah Alshowaeir, Regina Alvarenga, and others The Lancet Neurology Published: Sentember 27, 2022

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PERSONAL VIEW Myelin-oligodendrocyte glycoprotein antibody-associated disease

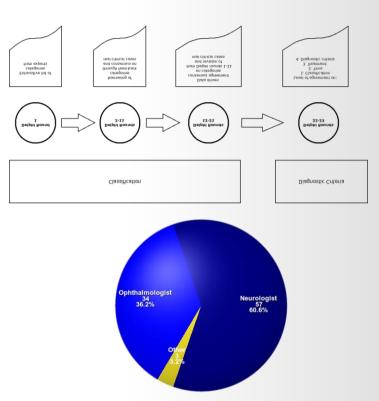
Romain Marignier, Yael Hacohen, Alvaro Cobo-Calvo, Anne-Katrin Pröbstel, Orhan Aktas, Harry Alexopoulos, and others *The Lancet Neurology*, Vol. 20, No. 9 Published: September, 2021

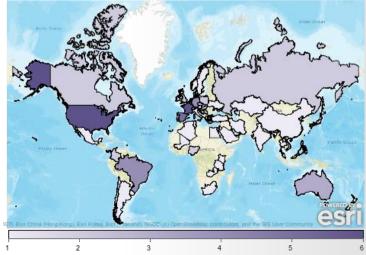
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REVIEW Mitochondrial disease in adults: recen advances and future promise

Yi Shiau Ng, Laurence A Bindoff, Gráinne S Gorman, Thomas Klopstock, Cornelia Kornblum, Michelangelo Mancuso, and

The Lancet Neurology, Vol. 20, No. 7 Published: July, 2021

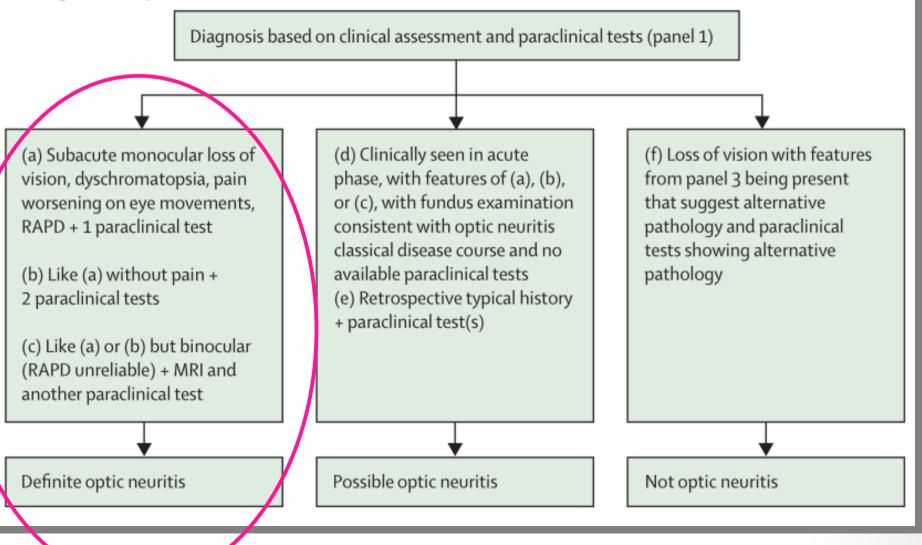




World wide distribution of number of experts

ICON 2022 Diagnostic Criteria

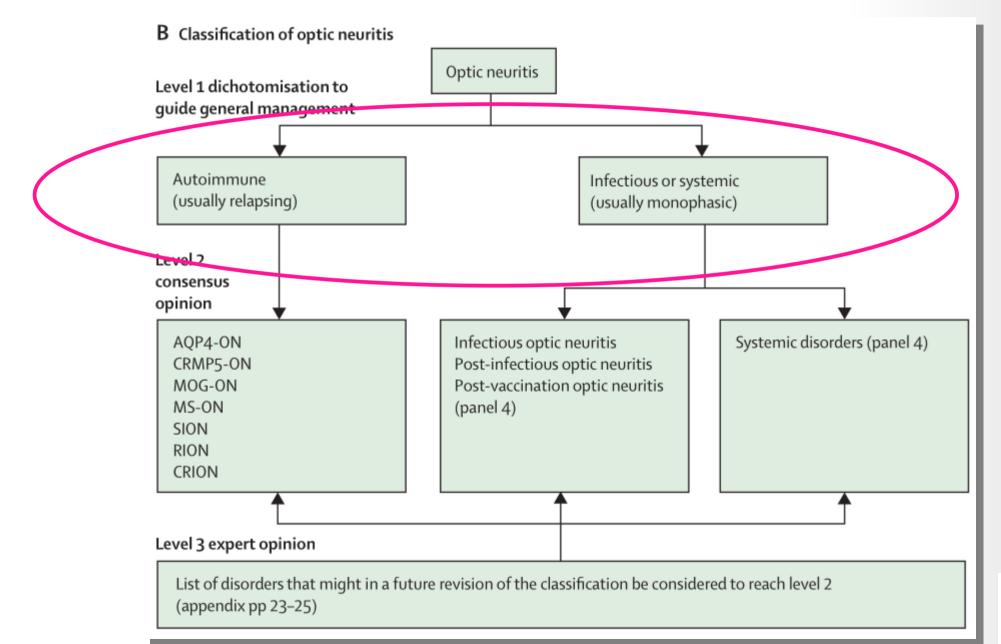
A Diagnosis of optic neuritis





TLN 2022

ICON 2022 Classification



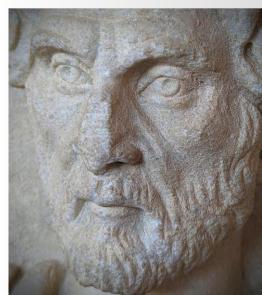


1st Case

- •34y old Caucasian female patient
- •7d RE pain, worsening on eye movements
- Dyschromatopsia & VA RE 6/9, LE 6/5
- •Right RAPD
- Reports: fatigue, cognitive problems, urinary incontinence, depression
- PmHx: right sided numbress lasting 1m, 3y ago
 MRI: DIS & DIT & 3 Gd+ non-symptomatic lesions

2nd Case

- 28y old, Afrocaribbean male
- Painless loss of vision LE (6/38)
- Dyschromatopsia
- L RAPD
- Several steroid responsive episodes over ~20y fup
- •OCT: pRNFL atrophy LE (IEPD >5%)
- •MRI a swollen, Gd+, left optic nerve. Brain & spinal cord normal
- •AQP4 seropositive





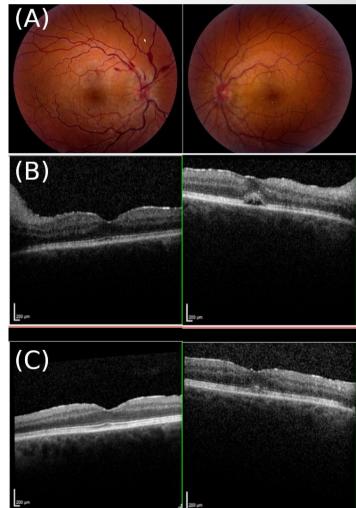
3rd Case

- •72 year old male develops febrile illness in Vietnam
- 2-3 weeks later bilateral, sequential, painless loss of vision (PL)
- no RAPD (but both pupils constrict with accomodation)

•Fundus:

- Bilateral disc edema
- •RE hemorrhages
- LE macular scar, CMO

•No recovery @ 6m fup (IVMP given ~6w after onset)



3 Scenarios

Case 1: is this MS ?

<u>Scenario A</u>: painful, monocular, subacute LOV, dyschromatopsia, RAPD

Case 2: is this NMO ?

<u>Scenario B</u>: no pain, monocular, subacute LOV, dyschromatopsia, RAPD

Case 3: what is this ?

<u>Scenario C</u>: binocular, subacute LOV, dyschromatopsia, no pain, RAPD unreliable

Panel 1: Diagnostic criteria for optic neuritis

Clinical criteria

- A: Monocular, subacute loss of vision associated with orbital pain worsening on eye movements, reduced contrast and colour vision, and relative afferent pupillary deficit
- B: Painless with all other features of (A).
- C: Binocular loss of vision with all features of (A) or (B).

Paraclinical criteria

- OCT: Corresponding optic disc swelling acutely or an inter-eye difference in the mGCIPL of >4% or >4 μm or in the pRNFL of >5% or >5 μm within 3 months after onset.
- MRI: Contrast enhancement of the symptomatic optic nerve and sheaths acutely or an intrinsic signal (looking brighter) increase within 3 months.
- Biomarker: AQP4, MOG, or CRMP5 antibody seropositive, or intrathecal CSF IgG (oligoclonal bands).

Application of the clinical and paraclinical criteria

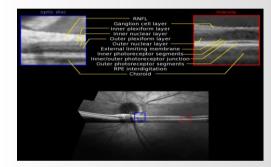
Definite optic neuritis

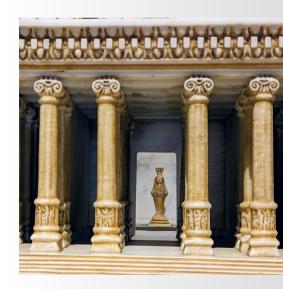
- (A) and one paraclinical test
- (B) and two paraclinical tests of different modality
- (C) and two different paraclinical tests of which one is MRI

Possible optic neuritis

- (A), (B), or (C) if seen acutely but in absence of paraclinical tests, with fundus examination typical for optic neuritis and consistent with the natural history during follow-up
- Positive paraclinical test or tests, with a medical history suggestive of optic neuritis

| Definite optic neuritis | Possible optic neuritis | Not optic neuritis | |
|---|---|--|--|
| 1 | <u> </u> | <u>†</u> | |
| (a) Subacute monocular loss of sixon, dyschromotopisa, pain worsening on ope movements, worsening of the second pain + 2 parachimical tests (2) Like (a) of (b) but bioscular (2) Like (a) (b) but bioscular (2) Like (a) Like | (d) Chinizally seen in acute phase, with fourture of (a), (b), or (c), with fundar examination constater with oppic neurition dascard floase course and no available paradimical trists (c) Shoropective typical history + paradimical test(p) | (f) Loss of vision with features from punel Sheng present that sugget alernative pathology and paradimical test showing alternative pathology | |
| Diagnosis of optic neuritis Diagnosis bas | ed on clinical assessment and paraclinical | tests (panel 1) | |
| Disangeie of ontic nauritie | | | |
| | | | |
| | | | |
| | | | |





TLN 2022

OCT in MS-ON

| | | | | | | | | | Mean difference* | 7 |
|--|--------------|----------------------------------|-------------------|--------------------|-------|-----------|-----------------------------|---------------|---------------------------|---|
| | Device | MSON | | Control | | | Weight (%) | | (µm; 95% CI) | |
| | | Mean (µm; SD) | Total eyes | Mean (µm; SD | D) To | otal eyes | | | (J) | |
| Peripapillary RNFL | | | | | | | | | -15-30 (-17-54 to -13-06) | |
| Balk et al (2014) ²¹ | н | 76-4 (11-6) | 144 | 91.7(6.8) | | 126 | 7.3 | - | -10-00 (-15-53 to -4-47) | |
| Behbehani et al (2015) ²² | т | 101-3 (14-4) | 32 | 111.3 (8.7) | | 51 | 5.8 | | -12-90 (-21-83 to -3-97) | |
| Behbehani et al (2016) ²³ | Z | 82 (14-1) | 10 | 94-9(6) | | 40 | 41 | | | |
| Esen et al (2016) ³⁵ | Z | 82.2 (11.8) | 40 | 96-7(8-2) | | 60 | 6-5 | - | -14-50 (-18-70 to -10-30) | |
| Feng et al (2013) ²⁶ | Z | 71-8 (19-2) | 12 | 102.1 (8.1) | | 28 | 3.2 🔸 | | -30.30 (-41.57 to -19.03) | |
| Gelfand et al (2012) ³⁰ | н | 80.2 (17.8) | 262 | 101-3 (10-1) | | 106 | 7.1 | - | -21.10 (-23.99 to -18.21) | |
| Gonzalez-Lopez et al (2014) ³¹ | Z | 79-6 (13-6) | 36 | 99-3 (8-7) | | 140 | 6-2 | | -19-70 (-24-37 to -15-03) | |
| Huang-Link et al (2015) ³⁴ | Z | 67.7 (7.91) | 15 | 93.6(8.9) | | 68 | 6-3 | - | -25-90 (-30-43 to -21-37) | |
| halil et al (2016) ³⁶ | 0 | 84.1 (13.5) | 30 | 117-8(26-2) | | 23 | 3.1 | | -3370 (-45-45 to -21-95) | |
| ange et al (2013) ⁴⁰ | H | 73.9 (15.2) | 13 | 98-4(8-8) | | 100 | 4.3 | <u> </u> | -2450 (-3294 to -1606) | nDNEL atranhy |
| berwahrenbrock et al (2012)43 | Н | 77-8 (14-6) | 183 | 100-6 (8-8) | | 183 | 7.2 | - | -22-80 (-25-27 to -20-33) | pRNFL atrophy |
| Oberwahrenbrock et al (2013)6 | H | 82-1 (18) | 16 | 101-4 (7-4) | | 90 | 41 | | -19·30 (-28·25 to -10·35) | 1 1 2 |
| Park et al (2014) ⁴⁴ | H | 70-1 (6) | 15 | 100-1 (9-3) | | 24 | 6-2 | • | -30-00 (-34-80 to -25-20) | |
| Rebolleda et al (2011) ¹⁶ Schneider et al (2013) ⁴⁹ | Z H | 81(0) | 18 | 93-5(0) | | 18 | | | Not estimable | |
| Soufi et al (2015) ⁵¹ | T | 85-3 (13-3) | 20 | 100-1 (10-8) | | 34 | 5.1 | | -14-80 (-21-67 to -7-93) | |
| Sycet al (2012) ⁵⁴ | 7 | 77 (11) | 7 | 104(8-7) | | 58 | 4.3 - | | -27.00 (-35.45 to -18.55) | |
| Walter et al (2012)55 | Ĥ | 78-7(11-7) 78-4(13-6) | 73 | 93-4 (10-4) | | 100 | 6.9 | - | -14-70 (-18-07 to -11-33) | |
| (uet al (2016) ⁵⁶ | z | | 87 | 92-9 (9-9) | | 61 | 6.7 | - | -14-50 (-18-29 to -10-71) | TINGOAD |
| Total(N) | £ | 73-6(14-8) | 35 | 97.1 (11.5) | | 41 | 5.5 | - | -2250(2354 0 12 16) | TLN 2010 |
| Heterogeneity: τ ² =23·83; χ ² =97·35 | r df 17/- | 0.00041 # 02.0 | 1030 | | 1 | 1333 | 100-0 | • | -20-10 (-22-76 to -17-44) | |
| Test for overall effect: Z=14-82 (p- | 5, dt=1/ (p- | :0-0001); /~=83% | | | | | | · · | | |
| Test for overall effect: Z=14-82 (p- | <0.0001) | | | | | | | -20 -10 0 | 10 20 | |
| Tert for overall effect 7=14-82 (D | <0.0001) | | | | | | | | | |
| Heterogeneity: t [*] =23.83; X [*] =97.3! | 5, df=17 (p- | 0.0001); I*=83% | | | | | | -20 -10 0 | 10 20 | 20 10 $(17$ 11 20 70 100 |
| Total(N) | | | 1030 | | 7 | 1333 | | | (OF % CI) | <u>20.</u> 10 (17.44-22.76) μm |
| Xu et al (2016) ⁹⁶ | Z | 73-6(14-8) | 32 | | | | | Mean differen | e (95% C) | |
| Syc et al (2012) ⁵⁶ Walter et al (2012) ⁵⁵ | н | 1 million | | Control | | Weight | | | | |
| Soufi et al (2015) ²⁶ | 2 | MS | ON | | | | | | | |
| Schneider et al (2013) ⁴⁹ | 1 | Me | an (SD) Total | Mean (SD) | Total | | | | -28.93 (-40.41 to -17.45) | |
| Rebolleda et al (2011) ⁴⁶ | H | me | antes | | | 3.6% | | | -19.00 (-22.83 to -15.17) | |
| Park et al (2014) ⁴⁴ | Albeach | tt (2007)4 74 | 47 (22.15) 21 | 103-4 (10-96) | | | | | | |
| (2013) berwährenbrock et al (2013) | | | 2(16-2) 73 | 105.2 (9.4) | 406 | 11.6% | - | | -18.80 (-21.30 to -16.30) | TINIOQAZ |
| Oberwahrenbrock et al (2012)* | H Bock (2 | | | 104.5 (10.7) | 219 | 13.8% | + | | | TLN 2017 |
| ange et al (2013)** | Burkho | | | | 72 | 9.7% | | | -20.00 (-25.03 to -14.97) | |
| (halil et al (2016)" | Fisher | 2006)10 85 | (17) 63 | | | | | | -31.60 (-41.37 to -21.83) | |
| tuang-Link et al (2015) ¹⁴ | Frohm | an (2009) ¹¹ 70 | 3(13-4) 12 | 101.9 (8.9) | 8 | 4.6% | | | -19.50 (-25.85 to -13.15) | |
| Sonzalez-Lopez et al (2014) | Kliston | ter (2008) [≤] 84 | 5(15-1) 32 | 104 (9-2) | 25 | 7.8% | | | -19.50 (-25.05 (0-15.15) | |
| 2012000 0120 (2022). | H Merie (| | 85(24.12) 30 | 106-24 (12-46) | 46 | 4.9% | | | -22.39 (-31.74 to -13.04) | 2020(17012000) |
| eng et al (2013)** | 20 | | | | | | | | Not estimable | <u>20.</u> 38 (17.91-22.86) μm |
| sen et al (2016) ⁸ | | | 46 () 25 | | 25 | ** | | | | |
| | Pulicke | n (2009) ²⁰ 84 | 2(14-7) 82 | 102.7 (11.5) | 94 | 11.4% | | | -18.50 (-22.44 to -14.56) | |
| | Ratchfi | ord (2007)21 88 | 3(16-5) 157 | 102.4(11) | 77 | 12.1% | | | -14.10 (-17.66 to -10.54) | |
| | Sepula | re (2007) ²⁰ † | ··(··) 24 | 92.3 (16.7) | 58 | | | | | |
| | Siger (2 | and a second second | | | | | | | Not estimable | |
| | 1000 | | | 100.3(12.1) | 24 | 6.7% | | | -16.38 (-23.68 to -9.08) | |
| | Trip (20 | | 7(18-8) 25 | 102.9 (14.6) | 15 | 4.2% | | | | Decrease Increase |
| | Zaveri | 2008)35 81 | 8(19-3) 68 | 104.6 (10.3) | 85 | 9.6% | | | -3420 (-44.64 to -23.76) | 20- |
| | Total | | 956 | S. | | | | | -22.80 (-27.88 to 17.77) | MSON versus control |
| | Testfo | heterogeneity: r ¹ =9 | 91- x2=28.02 df | 11 (p=0-003); P=61 | 1107 | 100.0% | ٠. | | | - |
| | Test fo | overall effect: Z=16- | 14/n - 20-03, dis | 11 (p=0-003); P=61 | .% | | • | | -20.38 (-22.86 to -17.91) | 15- MSNON versus MSON |
| | | evenuencer v=10- | 14 (p<0.0001) | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | -50 | -25 | | | lo- I _ I I I I I I I I I I I I I I I I I |
| | | | | | | -50 | -2.5 | 0 25 | 50 | |
| | | | | | | -50 | -25 Favours experimental | 45 | 50 | |
| | | | | | | -50 | Favours experimental | Favours co | ntrol | |
| | | | | | | -50 | -2.5 | 45 | ntrol | |

pRNFL GCIPL mRNFL INL

ONPL

4th Case

•37y old woman 18 month ago
•expanding central scotoma
•Periocular pain, score 9/10
•Photo phobia

Headaches improved with topiramate

•Visual function with 3 more attacks:

BCVA RE 6/9.5, LE 6/24

Normal colour vision

Left RAPD

^{4th} Case

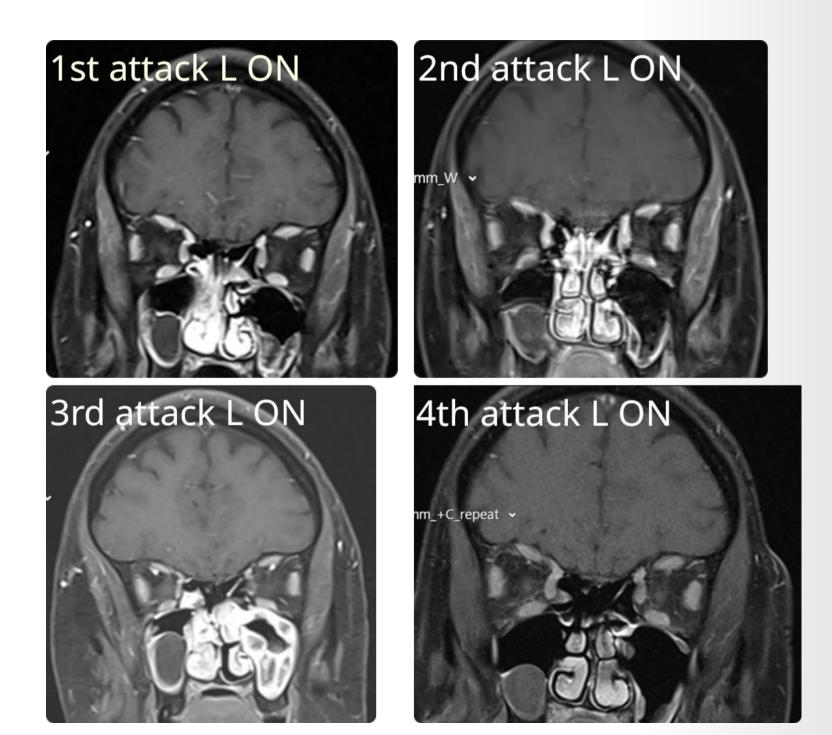
<u>PmHx:</u>

- Recurrent oral ulcers for 9 years
- Erythematous digital nodules & facial rash
- Musculoskeletal pain & fatigue
- •GI problems (bloating, diarrhoea, steatorrhoea)

Management in referring hospital:

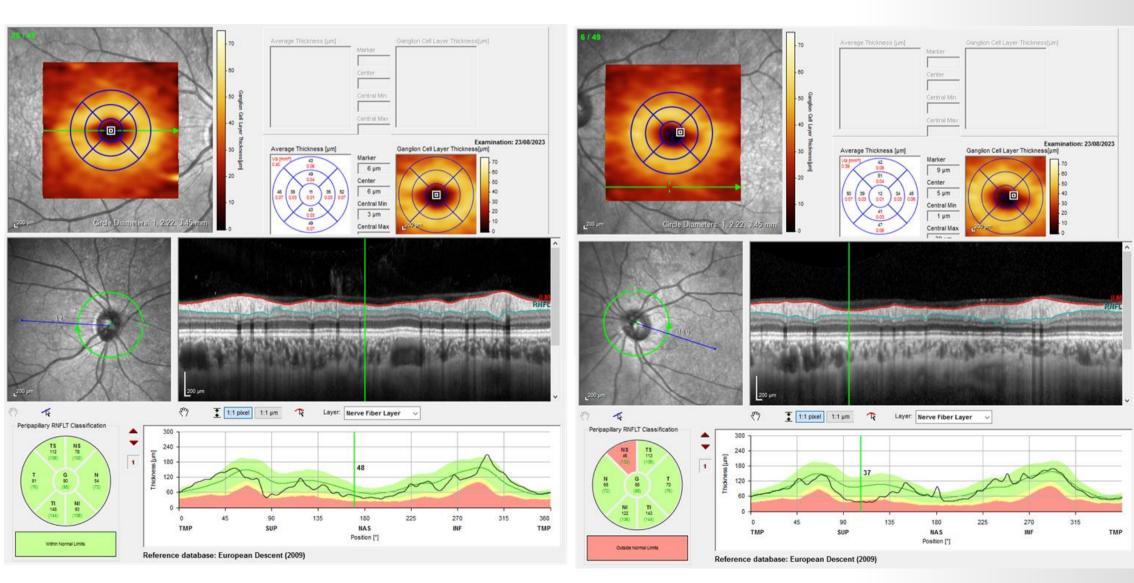
 High dose IV corticosteroids repeatedly for suspected relapsing optic neuritis
 & repeat MRI

MRI



OCT

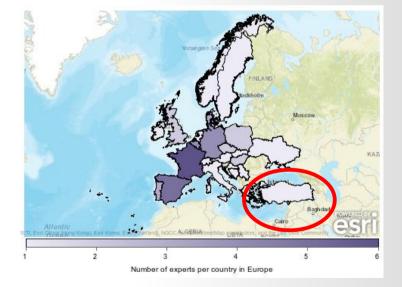
IEPD macular = 2.5% (less than the 4% required) IEPD disc = 3% (less than the 5% required)



4th Case

ICON 2022: not optic neuritis Not clinically Not with para-clinical tests

 Dx: acute L superior BRVO pattern recognition on OCT



- •DD: Behçet's disease
- National Behçet's Centre @Birmingham

Outlook





REVIEW

Artificial intelligence extension of the OSCAR-IB criteria

Axel Petzold^{1,2}, Philipp Albrecht³, Laura Balcer⁴, Erik Bekkers⁵, Alexander U. Brandt⁶, Peter A. Calabresi⁷, Orla Galvin Deborah⁸, Jennifer S. Graves⁹, Ari Green¹⁰, Pearse A Keane¹, Jenny A. Nij Bijvank², Josemir W. Sander^{11,12,13}, Friedemann Paul¹⁴, Shiv Saidha⁷, Pablo Villoslada¹⁵, Siegfried K Wagner¹, E. Ann Yeh¹⁶, the IMSVISUAL, ERN-EYE Consortium^a

Neurology[°] Neuroimmunology & Neuroinflammation



November 2023; 10 (6) RESEARCH ARTICLE OPEN ACCESS

The OSCAR-MP Consensus Criteria for Quality Assessment of Retinal Optical Coherence Tomography Angiography

Bebecca Wicklein, Charmaine Yam, Christina Noll,
 Lilian Aly, Nicolas Banze, Eva Feodora Romahn, Elisabeth Wolf,
 Bernhard Hemmer,
 Frederike C. Oertel,
 Hanna Zimmermann,
 Philipp Albrecht, Marius Ringelstein, Carmen Baumann,
 Nikolaus Feucht, Josef Penkava,
 Joachim Havla, Jonathan A. Gernert, Christian Mardin,
 Eleni S. Vasileiou,
 Anneke Van Der Walt,
 Omar Al-Louzi, Sergio Cabello,
 Angela Vick-Jordana, Julia Krämer,
 Heinz Wiendl,
 Jana Lizrova Preiningerova,
 Olga Ciccarelli,
 Elena Garcia-Martin, Veronika Kana,
 Peter A. Clabresi, Friedemann Paul,
 Shiv Saidha,
 Axel Petzold,
 Ahmed T. Toosy,
 Benjamin Knier, ; on benalf of IMSVISUAL Consortium

5th case

- 32 year old woman with RRMS
- Natalizumab for > 10 years
- Develops progressive cloudy vision in right eye
- Started on corticosteroids for suspected MS-ON
- MRI: no enhancement of right optic nerve, no new lesions
- Vision continues to worsen (HM)
- 22 days after onset seen @MEH
- OCT: ...



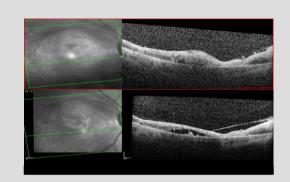
nature, September 2018 VOL 24 NO 9 WWW.mature com/raturemedicine

Al accelerates diagnosis NAD⁺ biosynthesis and high-risk hospitalizations Targeted microbiome therapy for thrombosis

| e Refer | ral suggestion (%) |
|------------------|--------------------|
| Urgent | 98.9 |
| Semi-urgeni | 0.5 |
| Routine | 0.4 |
| Observation only | 0.2 |



OCT & AI



- 5th case: VZV vitritis
- Observation: 1.71%
- Routine: 24.09%

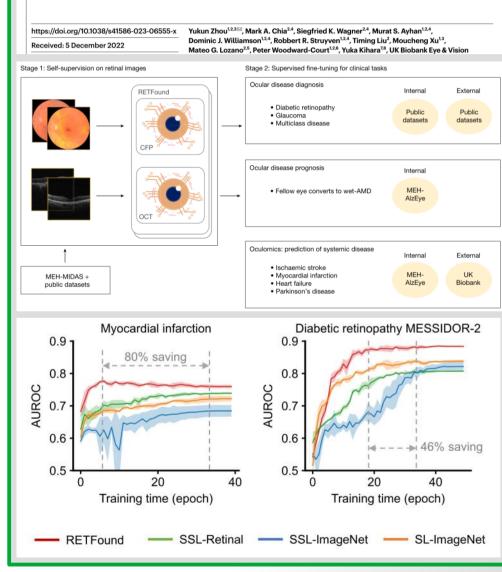
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- Semi-Urgent: 46.39%
- Urgent: 27.80%

Article

A foundation model for generalizable disease detection from retinal images



Nature Medicine 2019

Summary

Clinical approach to ON differential diagnosis
ICON 2022 Diagnostic Criteria
ICON 2022 Classification
5 Cases: 4 not MS-ON

3 clinical scenarios

Outlook: AI, pattern recognition,

non-supervised learning, EUNOS 2024







Teşekkürler ederim





