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"White dot syndromes", an inappropriate and outdated misnomer

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Along the years, examples of drifts in medical thought were not so rare. Approximative and imprecise views or inconsiderate notions are voiced by opinion leaders in high-impact journals, which can negatively affect the appraisal of a disease or a group of diseases for years or decades.

The period from the late 1960s to the early 1990s was particularly productive as far as the description of new diseases in posterior uveitis is concerned. Astute clinicians, based on sharp phenomenological observations gave precise disease defining criteria on numerous "new" conditions. In 1968, Gass described acute posterior multifocal placoid pigment epitheliopathy (APMPPE) [1], followed in 1969 by the description of multifocal choroiditis (MFC) [2], renamed a few years ago Idiopathic Multifocal Choroiditis by a group of experts [3]. In 1980, Ryan and Maumenee published an article on 13 patients affected by a disease they named Birdshot Retinochoroidopathy [4]. One year later, Donald Gass described 11 patients with the same clinical presentation which he called Vitiliginous Chorioretinitis [5]. In 1984 Jampol and Sieving made a very clear and

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substantiated definition of multiple evanescent white dot syndrome (MEWDS) [6]. In 1990 and 1992 Donald Gass again, respectively, described acute syphilitic posterior placoid chorioretinitis (ASPPC) [7] and acute zonal occult outer retinopathy (AZOOR) [8]. Beside these entities, there was a hypertrophic collection of putative new sub types of choroidal inflammatory diseases.

The common characteristics of the cited diseases were (1) resembling fundus lesions and (2) the fact that they were choroidal diseases. Although descriptions were very precise, some authors refrained to give clinicopathological or pathophysiological explanations. Others put forward arguments that were only hypothetical conjectures. This is indeed comprehensible, as the choroid was ill-accessible to precise imaging at that time. Consequently, physicians felt supported by those hypotheses, apparently filling that gap created by the lack of knowledge of the mechanisms for most of them.

Therefore, when in 1995, an opinion article was published in a high-impact journal which proposed the unifying term "fundal white dots" assembling these different entities [9], this terminology was quickly adopted at large in articles and textbooks, including the American Academy of Ophthalmology in its Basic and Clinical Science Course (BCSC) in 2000. "White dot symdromes" (WDS), derived from this article, became the official denomination devoted to this heterogenous group of diseases.

Once again, such a classification was based on similar fundus characteristics and the assumption that the listed diseases were a "spectrum of a similar pathological process", which we currently know not being the case.

As we can see on the table reprinted from the article at the origin of the term WDS (Fig. 1), the listed diseases are not driven by the same pathophysiological process and the suspected aetiologies were conjectural or just incorrect, such as Vogt-Koyanagi-Harada disease (VKH) which was supposed to be viral, while there were clear indications towards an autoimmune disease already [10]. In this group, we find also diseases inappropriately listed, such as diffuse unilateral subacute neuroretinitis (DUSN) obviously out of place, as well as entities like discrete multifocal choroiditis (DMC) which did not withstand the trial of time, being insufficiently well defined. The result was a potpourri list of diseases that could not be classified together.

When the WDS terminology emerged merely based on the phenomenological appearance of diseases, explanations given could only be hypothetical even among those who described the diseases, as a fine exploration of the choroid was not available yet. Indeed, Donald Gass attributed the primary lesion site of APMPPE to the retinal pigment epithelium (RPE). This hypothesis was revised in 1972 by Deutman, who understood that the origin of that disease was choriocapillaris non-perfusion even before indocyanine green angiography (ICGA) was available, and he called it acute multifocal ischaemic choriocapillaritis (AMIC), in a fully justified manner [11].

In the early '90 s, ICGA gave for the first time access to choroidal compartment, followed later by other techniques such as enhanced depth imaging optical coherence tomography (EDI-OCT) and OCT angiography (OCT-A).

ICGA allowed for the first time, a fine analysis of the choroidal tissue thanks to the two fundamental biophysical properties of the indocyanine green (ICG) molecule, infrared fluorescence and macromolecular behaviour. Infrared fluorescence allowed to detect and show choroidal lesion bypassing the RPE barrier. Secondly, the large macromolecular complex formed by the high affinity binding of ICG to large serum proteins (98%) remains inside the large choroidal vessels, while physiologically egressing through the large fenestrations of the choriocapillaris to fill the choroidal compartment. ICGA showed the level of choriocapillaris perfusion and precisely identified

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Table 1 Clinical manifestations of white dots

Clinical diagnosis	*Aetiology*	*N*	*M/F*	*Vitreous haze*	*Degree of evanescence*	*Outcome**
SO	Autoimmune	17	11/6	++	+/−	Variable
VKH	?viral	11	3/8	++	+	Fair
APMPPE	?viral	9	3/6	+	+/−	Good
BSC	?immune	8	0/8	+/−	+/−	Poor
MEWDS	?	8	3/5	−	++	Good
PIC	?	3	0/3	−	+	Fair/good
DMC	?	12	2	+	+	Fair/poor
DUSN	Parasite	12	8/4	+	++	Fair/good

SO=Sympathetic ophthalmia. VKH=Vogt-Koyanagi-Harada disease; APMPPE=acute posterior multifocal placoid pigment epitheliopathy; BSC=birdshot choroidopathy; MEWDS=multiple evanescent white dot syndrome; PIC=punctate inner choroidopathy; DMC=discrete multifocal choroiditis; DUSN=diffuse unilateral subacute neuroretinitis.

Fig. 1 Table taken from Br J Ophthalmol. 1995; 79:856–60. Listing of conditions classified in the group of "fundal white dots". It is clear that the pathological process is not similar in these entities. DUSN, a clearly defined parasitic disease should not belong to this list and has a well-known infectious etiology and pathological course. Discrete Multifocal Choroiditis (DMC) is a condition that no more exists as an entity of its own. (Permission of reproduction of table granted by BJM)

choroidal foci which appear as dark spots indicating impaired ICG dye diffusion/filling, due to space-occupying lesions/foci [12] (Fig. 2).

Thanks to ICGA, it became possible to clarify the hidden pathophysiological mechanisms of these choroidal conditions. Nowadays, we recognize two

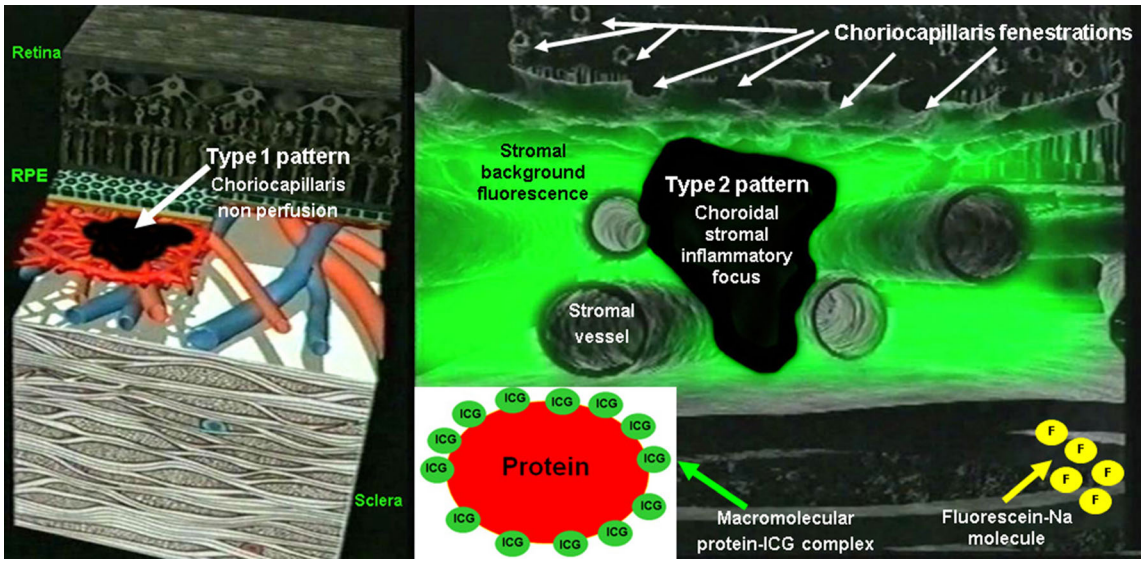

Fig. 2 Cartoons representing the two ICGA patterns and explain the two physiopathological mechanisms of non-infectious choroiditis. These angiographic signs allowed us to define and distinguish the two main mechanisms of choroiditis, (1) choriocapillaris non perfusion defining choriocapillaritis entities and hypofluorescent dark dots/foci defining stromal choroiditis. (reprinted from Herbort Jr CP, Mantovani A, Tugal-Tutkun, Papasavvas I. Classification of non-infectious and/or immune mediated choroiditis: a brief overview of the essentials. Herbort CP Jr, Mantovani A, Tugal-Tutkun I, Papasavvas I. Classification of Non-Infectious and/or Immune Mediated Choroiditis: A Brief Overview of the Essentials. Diagnostics (Basel). 2021 May 24;11(6):939. https://doi.org/10.3390/diagnostics11060939. PMID: 34,073,914; PMCID: PMC8225100.)

main disease categories: choriocapillaritis where the choriocapillaris is non-perfused and stromal choroiditis where the stromal choroidal tissue is affected, being infiltrated by inflammatory foci [13–15] (Fig. 3).

Each of the two main categories of inflammatory choroidal diseases was further subdivided into primary and secondary forms. Within the choriocapillaritis entities, the term of primary inflammatory choriocapillaropathies (PICCPs) was used when the trigger was not identified. Secondary choriocapillaritis includes syphilitic posterior placoid chorioretinitis (ASPPC), an immune mediated choriocapillaris non-perfusion triggered by syphilis, as well as tuberculosis-related serpiginous choroiditis resulting from the same mechanism. In both cases an identified pathogen triggers the inflammatory response. As far as stromal choroiditis is concerned there are also two sub-entities. The choroiditis can originate primarily and exclusively from the choroidal stromal structures in the form of an autoimmune reaction, which is the case for VKH disease, HLA-A29 birdshot retinochoroiditis and sympathetic ophthalmia. These conditions are called primary stromal choroiditis entities. In secondary stromal choroiditis, the choroid is only an innocent bystander of a systemic inflammatory condition that may involve its tissues, but not necessarily, such as observed in sarcoidosis chorioretinitis [16].

Therefore, the attempt made in the past to merge these conditions under the umbrella term of "fundal white dots" missed not only its purpose but also triggered a chain of misinterpretations at the origin of confusions on non-infectious choroiditis for the following almost 3 decades. Unfortunately, the uveitis specialist community quickly spread out the terminology, after this inaugural article. In one textbook, 26 conditions were cited including even Behçet's disease, giving an idea on how absurd and useless this concept was [17].

Time de facto showed on how "fundal white dots" was an inappropriate terminology, debunking the concept that those conditions listed share "a similar pathological process". Consequently, it is important to discriminate them on the base of their mechanisms and not based on their similar fundus aspects: we now know that MEWDS pathophysiology profoundly differs from HLA-A29 birdshot retinochoroiditis and has

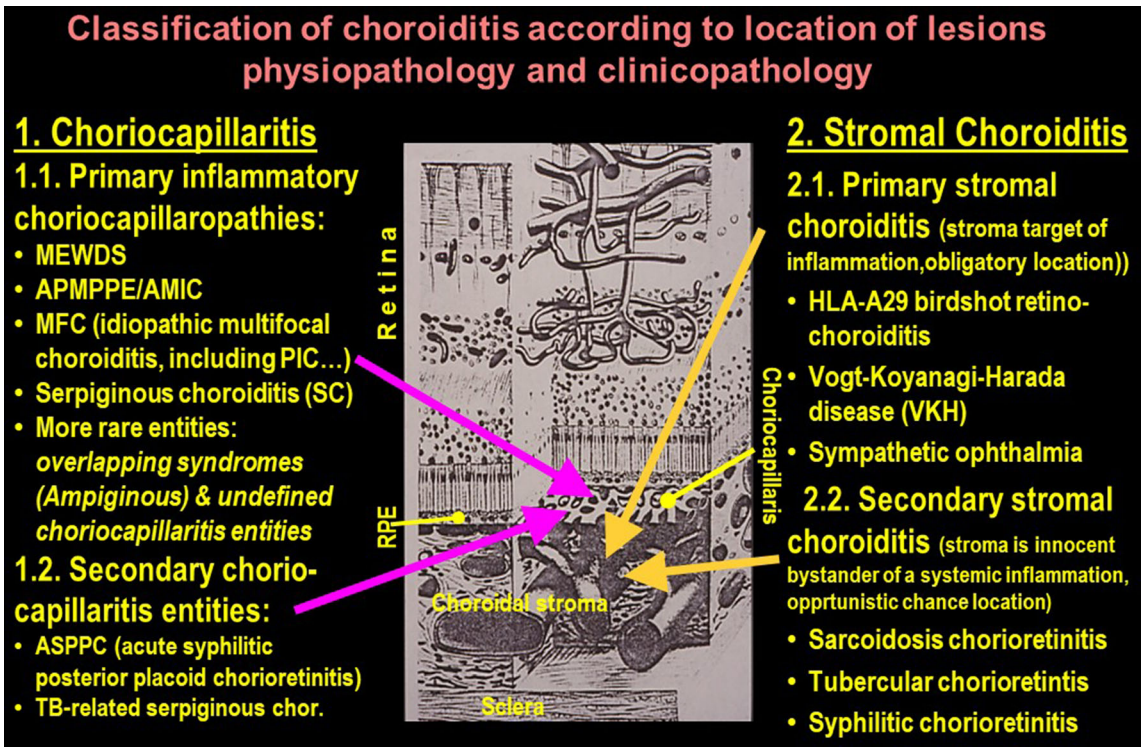

Fig. 3 Listing of the different non-infectious choroiditis entities. On the left, primary and secondary choriocapillaritis entities. On the right, primary and secondary stromal choroiditis entities

nothing to share with it. This group of conditions has not only a different pathophysiology, but also different clinical courses and features, leading again to different ancillary testing for follow-up. Therefore, it is time to replace an inappropriate misnomer by the classification proposed and once again debunk the myth upheld against the evidence provided by the pioneering pragmatism of several clinicians along these years. However, this notion is so ingrained in the uveitis terminology that it is very hard nowadays to get rid of it. Consequently, that nomenclature is embedded in medical web search engines, biasing the search on a given disease.

For instance, when searching the term "MEWDS", about 20% of the items come up concern birdshot retinochoroiditis and many more concerns other "WDS entities", since internet search engines erroneously merged them based on the previous classification.

The numerous studies performed in the past on "white dot syndromes" appear as meaningless, as they include diverse diseases that should not be analysed together. Even today, it is not rare to read articles still published ignoring the scientific advances made across the years and still biasing the correct interpretation of the disease's nature and the treatment, consequently [18].

We truly believe that a paradigm shift is necessary to drive the correct interpretation of choroidal diseases, leading to a new course of the medical literature driven by precise quantification and measurement of choroidal inflammation [19], targeting a correct interpretation and therapeutic approach.

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