Principles and Practice of Clinical Electrophysiology of Vision

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Albinism

Patricia Apkarian

Albinism is a hereditary disorder of the melanin pigment system in which the normal histogenesis of the developing retina and optic stalk are precluded. The aberrant pigment cell structures interfering with the development of these two neural ectoderm derivatives results in a sequela of visual system anomalies, including foveal hypoplasia and retinal fiber misprojections. Nystagmus, iris diaphany, fundus hypopigmentation, high refractive error, and strabismus are also characteristic albino features.[15] In addition to ocular anomalies, neural crest derivatives such as the skin and hair also may be affected and show varying degrees of hypopigmentation. In this latter condition, the skin typically burns following sun exposure, and there is also a high risk of skin cancer.

As shown in Figure 108–1, Plate 28, the genotypic and phenotypic expression in albinism varies widely, and while several other inborn errors of metabolism may effect varying degrees of dermal and ocular hypopigmentation, all forms of albinism show foveal hypoplasia and a preponderance of ipsilateral retinal fiber decussation that disrupts retinotopic organization throughout the visual pathway. The latter is pathognomonic to albinism and can be readily detected by visual evoked potential (VEP) examination of the potential distribution across the occiput following appropriate stimulus and recording conditions as described in Chapter 54. Based on pedigree analysis, biochemical assay of tyrosinase activity, and skin biopsy, the four albinos depicted in the left and center columns of Figure 108–1 have been classified as autosomal recessive oculocutaneous albinos: tyrosinase-negative (left) and tyrosinase-positive (center), respectively. The two albinos with dark hair are siblings and are typed as having X chromosomal ocular albinism. All of these albinos show clear evidence of VEP misrouting as depicted in Figure 108–2, where contralateral asymmetry in the raw traces as well as in the VEP topography plots (see Chapter 54 for more detail) is clearly evident regardless of genotype. Note also that one albino shows a right hemispheric response dominance following full-field binocular stimulation while the other shows a left hemispheric response dominance. Despite the hemispheric biases, following monocular stimulation the nondominant eye and occipital hemisphere reflect the appropriate contralateral asymmetry.

The major difficulty in the detection and differential diagnosis of albinism is that for a given albino, not all symptoms, either ophthalmological or cutaneous, may be manifested, whereas several may for a nonalbino. While foveal hypoplasia and the behavioral correlate of reduced visual acuity are obligate features, it is not uncommon for an albino to have relatively normal fundus pigmentation, no iris diaphany or photophobia, and/or no nystagmus. If, as in Figure 108–3, albinos without an expected symptom are compared with nonalbinos expressing the symptom, only the former show evidence of misrouting. This includes albinos with no nystagmus as compared with the nonalbino with congenital nystagmus (upper row), which is described in more detail below. Thus, despite the wide variation in

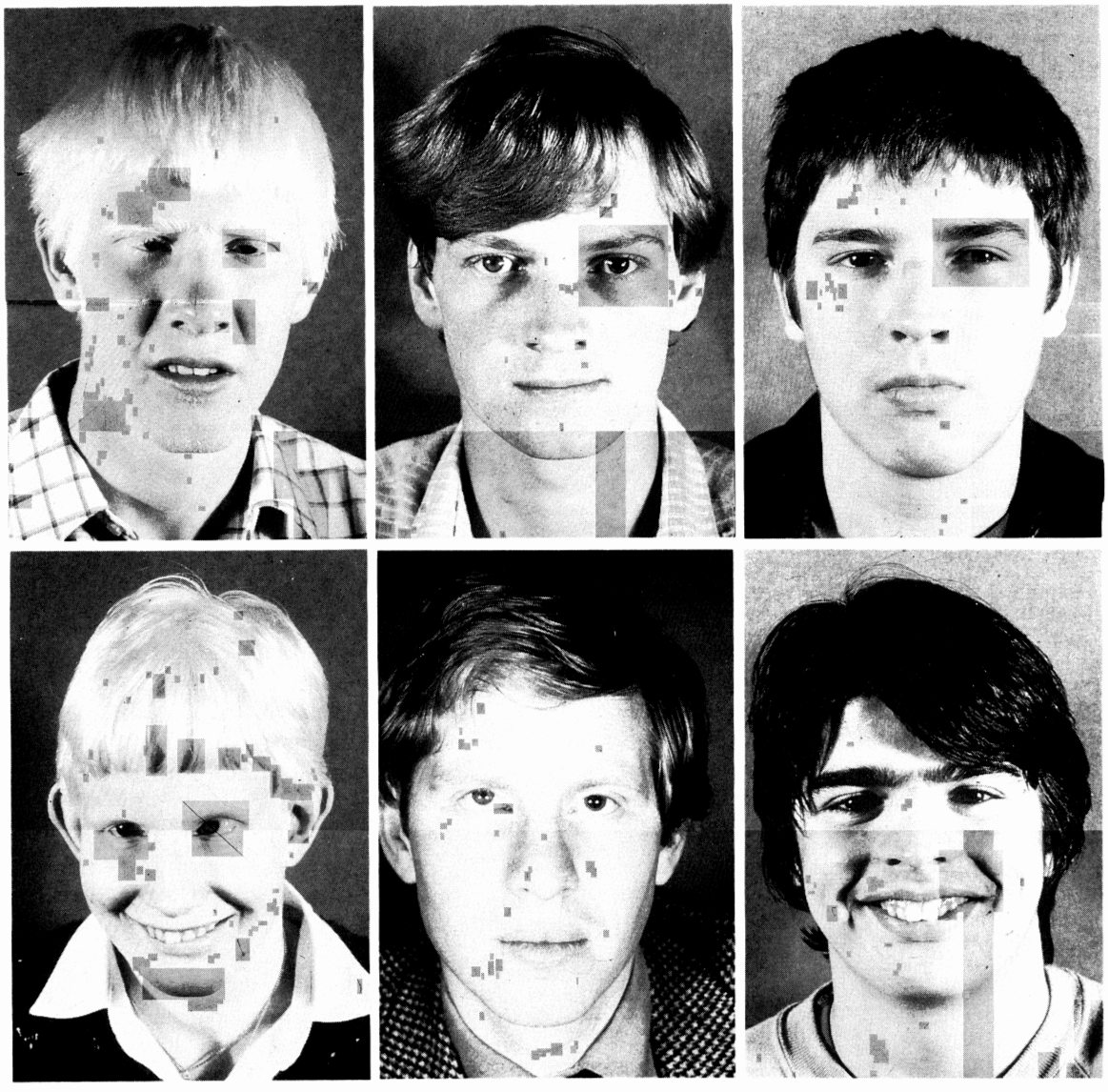


FIG 108–1.
Variable genotype and phenotype in a representative sample of albinos including autosomal recessive oculocutaneous (*left column*, tyrosinase negative; *center column*, tyrosinase positive) and X-chromosomal ocular albinos (*right column*). Foveal hypoplasia, reduced visual acuity, and VEP misrouting are common features regardless of mode of inheritance or phenotypic expression. (Adapted from Spekreijse H, Apkarian P: The use of a system analysis approach to electrodiagnostic (ERG and VEP) assessment. *Vision Res* 1986; 26:195–219. Used by permission.) **(See also Color Plate 28.)**

phenotypic expression not only between multiple genotypes but within a genotype as well, the VEP misrouting shows extraordinary sensitivity.[1]

While all albinos demonstrate VEP misrouting, heterozygote carriers characteristically do not, although some carriers show iris diaphany and retinal hypopigmentation. In Figure 108–4, the VEP response profile from an X chromosomal ocular albino carrier is presented along with the responses from her albino son. A partial family pedigree across four generations is depicted. The 39-year-old carrier presented with reduced acuity, significant iris diaphany, and patchy retinal pigmentation. However, there was no nystagmus, foveal and macular reflexes were normal, and the VEP misrouting test was negative as seen by inspection of the monocular responses following full-field stimulation of a large appearing/disappearing checkerboard pattern. As expected, the albino son (proband) who presented with nystagmus, fundus hypopigmentation, foveal

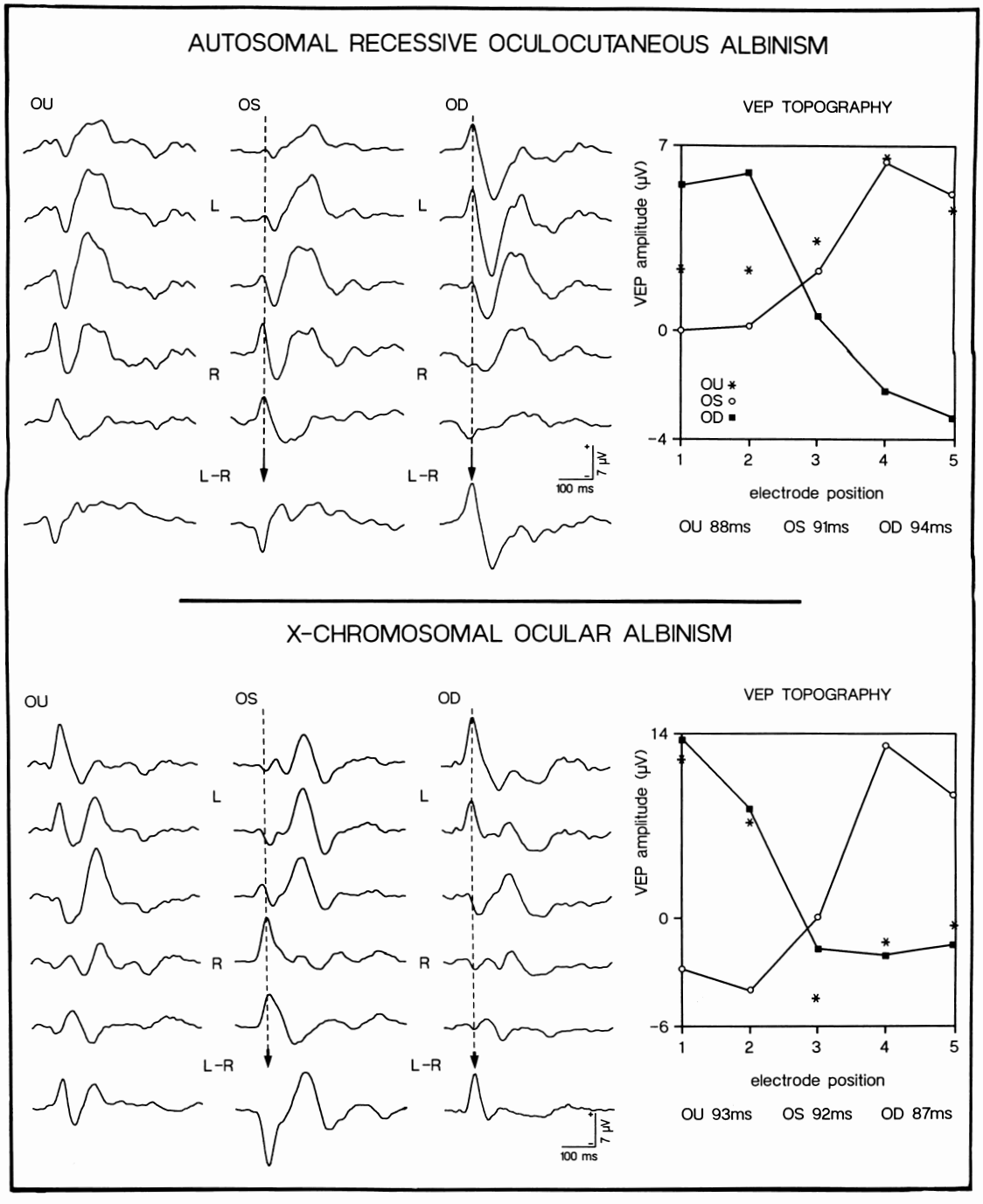


FIG 108–2.

Binocular *(OU),* left eye *(OS),* and right eye *(OD)* pattern-onset/offset (40/460 ms) responses of an oculocutaneous albino and an ocular albino. The *upper* five traces from each column represent responses derived from one of five electrodes positioned from the left hemisphere *(topmost trace)* to the right hemisphere *(trace 5);* the *bottom traces* represent a bipolar derivation obtained by subtracting trace 4 (R) from trace 2 (L). Note the change in sign at about 90 ms. The *vertical dashed lines* indicate the latency at which amplitudes were calculated for the VEP topography functions where binocular *(starred symbols),* left eye *(open circles),* and right eye *(closed squares)* amplitudes at about 90 ms are plotted as a function of electrode position from left (1, 2) to right (4, 5) occiput. Note that the interocular potential distributions show a crossed pattern. The oculocutaneous albino is the grandfather of the albino proband in Figure 108–5.

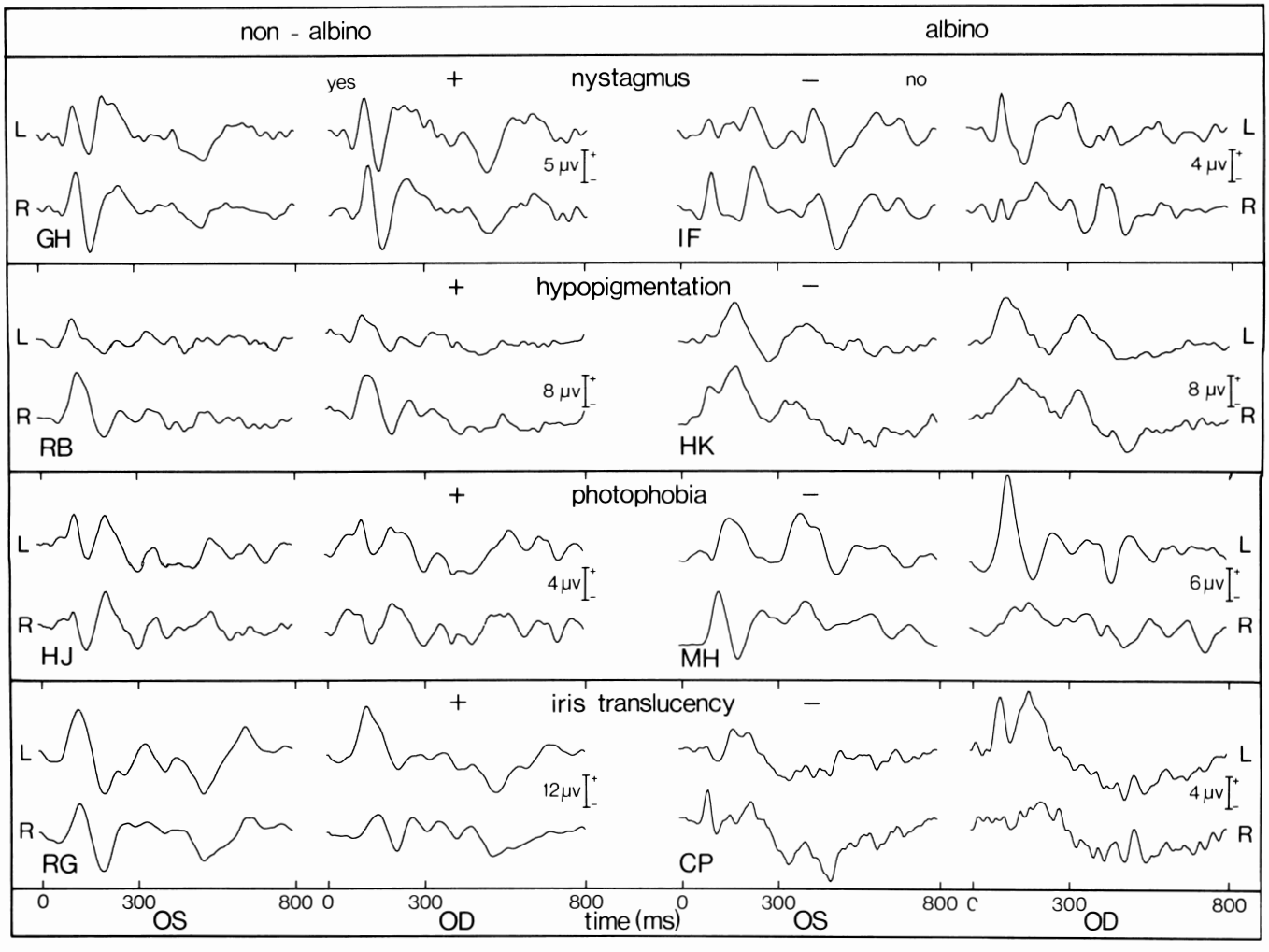


FIG 108–3.

Left eye *(OS)* and right eye *(OD)* pattern-onset/offset (300/500 ms) responses (check size, 55 minutes) in nonalbinos (columns 1 and 2) with the presence of the denoted albino symptom *(+)* and albinos (columns 3 and 4) with an absence *(–)* of the comparable symptom. The *upper traces* of each set represent a left *(L)* hemispheric derivation; the *lower traces* represent a right *(R)* hemispheric derivation. Note that for the nonalbinos, despite the presence of ophthalmological abnormalities symptomatic for albinism, the amplitude of the potential distribution from the left to the right hemisphere does not change with right to left eye stimulation. In contrast, contralateral asymmetry is seen for all albinos despite the absence of a common albino feature. (Adapted from Apkarian P, Spekreijse H: The VEP and misrouted pathways in human albinism, in Cracco RQ, Bodis-Wollner I (eds): *Evoked Potentials.* New York, Alan R Liss, Inc, 1986, pp 211–226. Used by permission.)

hypoplasia, iris diaphany, and photophobia showed clear VEP evidence of optic pathway misrouting for both the pattern onset and the luminance flash.

As shown in Figures 108–5 and 108–6, obligate heterozygotes for autosomal recessive forms of albinism also do not show the misrouting trait. A partial family pedigree of this genotype is presented in Figure 108–5 along with the flash responses of the proband who was tested at the age of 9 weeks. Clinical symptoms in this infant included fundus hypopigmentation, iris diaphany, nystagmus, photophobia, and a poorly defined macular reflex. The child also had white hair and very fair skin. The VEPs show optic pathway misrouting. The grandfather of this proband is also an albino and presented with all the classic features; accordingly, his VEP responses, presented in Figure 108–2 (upper traces), demonstrate the expected contralateral asymmetry of the monocular potential distributions from the left to right hemisphere. In contrast, the VEP profiles of

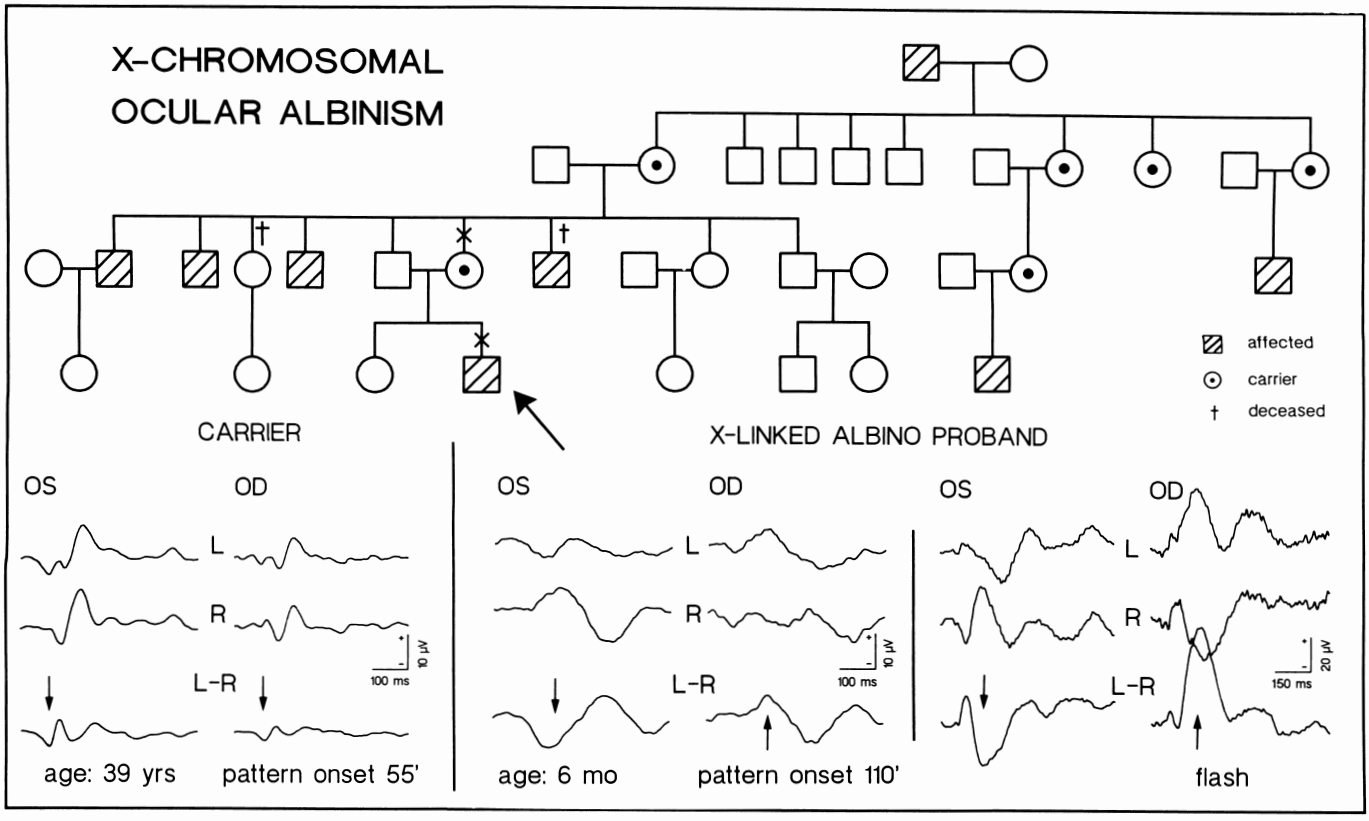


FIG 108–4.
Family pedigree of the X chromosomal mode of inheritance across four generations. VEP misrouting is not detected in the 39-year-old obligate heterozygote albino carrier *(lower left).* In contrast, the carrier's 6-month-old son who is the proband (see the *arrow* on the pedigree) shows the albino misrouting profile for both flash and pattern onset. Note that the immature responses do not show component-specific asymmetry but rather the whole positive peak appears to shift from the right to the left hemisphere following left and right eye stimulation, respectively. *Crosses* on the pedigree indicate the two family members tested. (From Apkarian P, Spekreijse H: The use of the electroretinogram and visual evoked potentials in ophthalmogenetics, in Desmedt JE (ed): *Visual Evoked Potentials.* Amsterdam, Elsevier Science Publishers, 1990, pp 169–223. Used by permission.)

proband's father (upper traces) and paternal aunt (lower traces) show no evidence of aberrant retinofugal projections (see Fig 108–6). Both show a strong left hemispheric response dominance (the aunt to a greater degree), but unlike their albino father, binocular, left eye, and right eye responses all lateralize to the left or at least show no interocular differences in their hemispheric topography. These negative misrouting findings in the human albino carrier are of interest in light of reports of abnormal retinogeniculocortical pathways in normally pigmented cats that carry a recessive albino allele.[12] However, to date there is no clear evidence indicating aberrant visual pathways in the human albino carrier, and as such, albino carrier detection with the VEP is not feasible.

That the VEP correlate of misrouted optic pathway projections is pathognomonic to albinsim has been challenged by reports of VEP misrouting in nonalbino patients, including those with congenital nystagmus, dissociated vertical deviation (DVD), and Prader-Willi syndrome.[9, 10, 13] As shown in Figures 108–3 (upper traces), 108–7, and 108–8 and in reports from several independent laboratories,[3–5, 7, 8, 11] these claims cannot be substantiated. Typically the erroneous conclusions stem from inadequate stimulus and recording conditions and a subsequent misinterpretation of the results. For example, in the studies purported to find VEP evidence of abnormal visual pathway projections in patients with congenital nystagmus, only the luminance-flash was employed. For patients with DVD, misrouting detection was attempted with half-field pattern reversal. The VEP correlate of abnormal

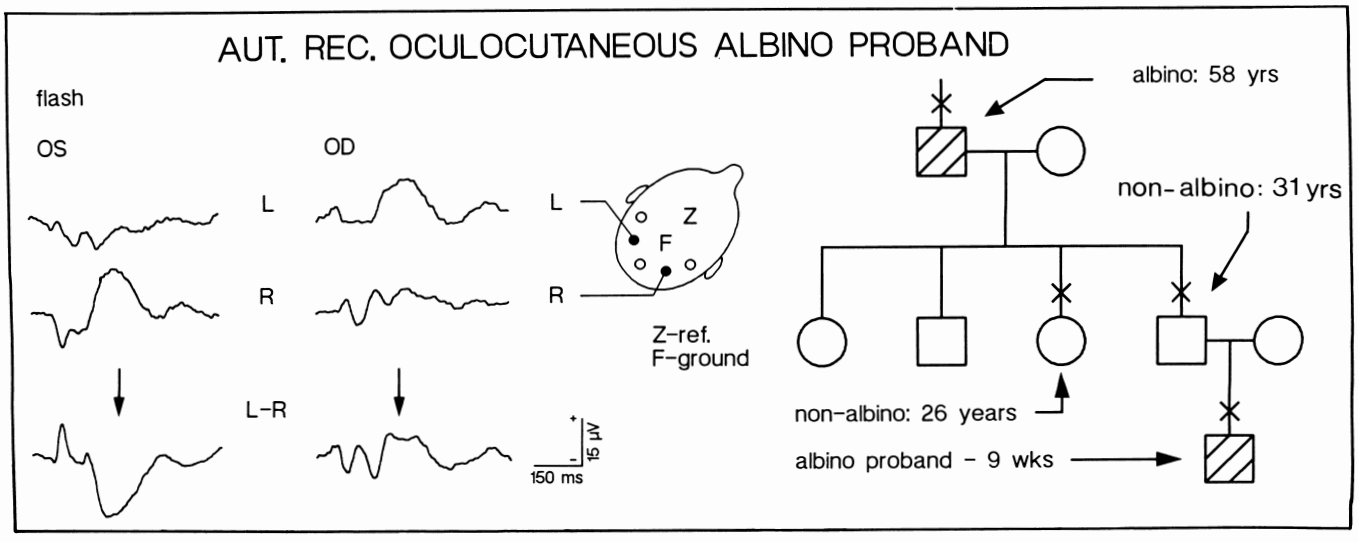


FIG 108–5.
Partial family pedigree of an autosomal mode of inheritance across three generations. *Crosses* indicate the four family members tested; *hatched squares* indicate the condition of albinism. Left eye *(OS)* and right eye *(OD)* luminance flash responses are depicted at the *left* for the 9-week-old albino proband. Traces are from the left *(L)* and right *(R)* hemispheric derivations depicted in the schematic. VEPs of the 58-year-old albino grandfather are presented in Figure 108–2. (From Apkarian P, Spekreijse H: The use of the electroretinogram and visual evoked potentials in ophthalmogenetics, in Desmedt JE (ed): *Visual Evoked Potentials.* Amsterdam, Elsevier Science Publishers, 1990, pp 169–223.. Used by permission.)

retinofugal projections is reliable only with full-field pattern-onset stimulation in the older albinos and luminance-flash in albino infants and toddlers. Figure 108–7 illustrates the more typical VEP response profile of a patient with DVD when tested with an appropriate protocol. For comparison, the VEPs from an age-matched albino are also presented. Component specificity in contralateral VEP asymmetry is observed in the monocular VEPs of albinos within this age range (8 to 9 years). Despite the immature waveform, the albino shows the albino VEP hemispheric crossover within a latency window around 90 ms. At a comparable latency the monocular VEPs of the DVD patient show no interocular difference in hemispheric lateralization. This negative misrouting profile does not alter even if the potential distribution is examined at a longer latency.

The conflicting reports concerning VEP misrouting in patients with Prader-Willi syndrome is somewhat more complicated. Prader-Willi syndrome is characterized by infantile hypotonicity, hypogonadism, hyperphagia, and mental retardation. Secondary features include chromosome mutations, particularly of the proximal long arm of chromosome 15, and pigment anomalies including iris diaphany fundus hypopigmentation, and skin hypopigmentation. Some authors purport a correlation between hypopigmentation, chromosome 15q deletion, and neural ectoderm anomalies comparable to those observed in albinism.[9, 16] If patients with Prader-Willi syndrome also show VEP evidence of an aberrant optic pathway, the correlation is supported. Unfortunately, regardless of the presence or absence of hypopigmentation, chromosomal anomalies, and/or ophthalmic symptoms including strabismus, reduced acuity, and foveal hypoplasia, patients with Prader-Willi syndrome test negative for albino misrouting, typically showing the VEP response profile presented in Figure 108–8. Inspection of the VEP traces shows that following right eye stimulation, the major positive response appears, as in albinism, to lateralize to the left hemisphere. However, following left eye stimulation, the potential distribution does not alter. Note from the difference potential that hemispheric asymmetry is present but there is no polarity inversion in the right to left eye derivations. While these responses show that patients with Prader-Willi syndrome do not evince the albino optic pathway anomaly, this patient group does present with a curious VEP topography that takes the form of a striking midline response minimum regardless of the eye of stimulation. A midline response negativity is not unique to the Prader-Willi syndrome, although its unusually high incidence, the etiology of

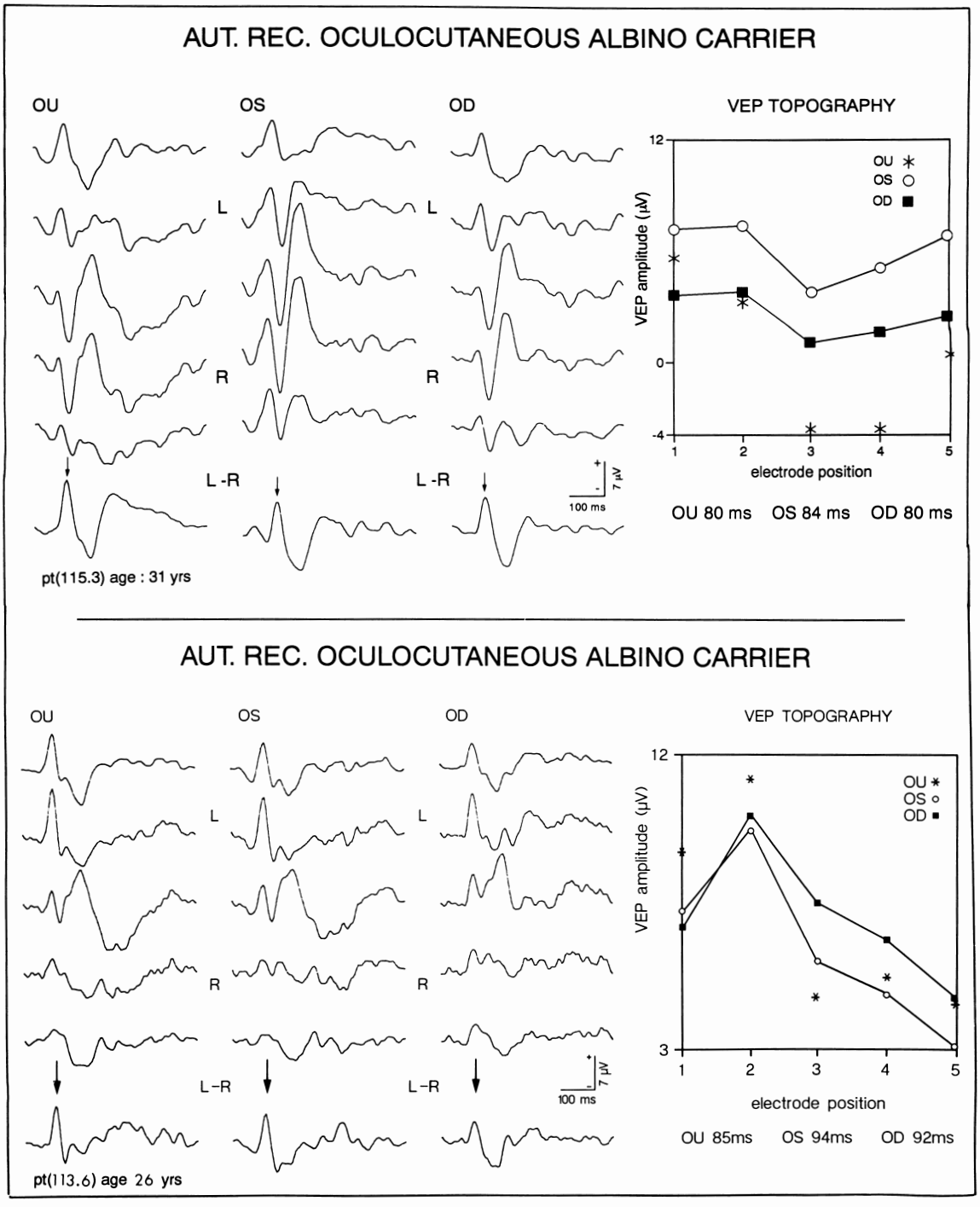


FIG 108–6.
Binocular *(OU),* left eye *(OS),* and right eye *(OD)* pattern-onset/offset (40/460 ms) responses from two obligate heterozygotes including the father *(upper traces)* and aunt *(lower traces)* of the albino proband depicted in Figure 108–5. VEP amplitudes at the latencies indicated (see the *arrows* also) are plotted as a function of electrode position. Both carriers show a left-hemispheric response dominance, and the 31-year-old carrier also shows an interocular amplitude difference with *OS* greater than *OD.* Despite the hemispheric dominance and interocular differences, neither of these family members shows VEP albino misrouting.

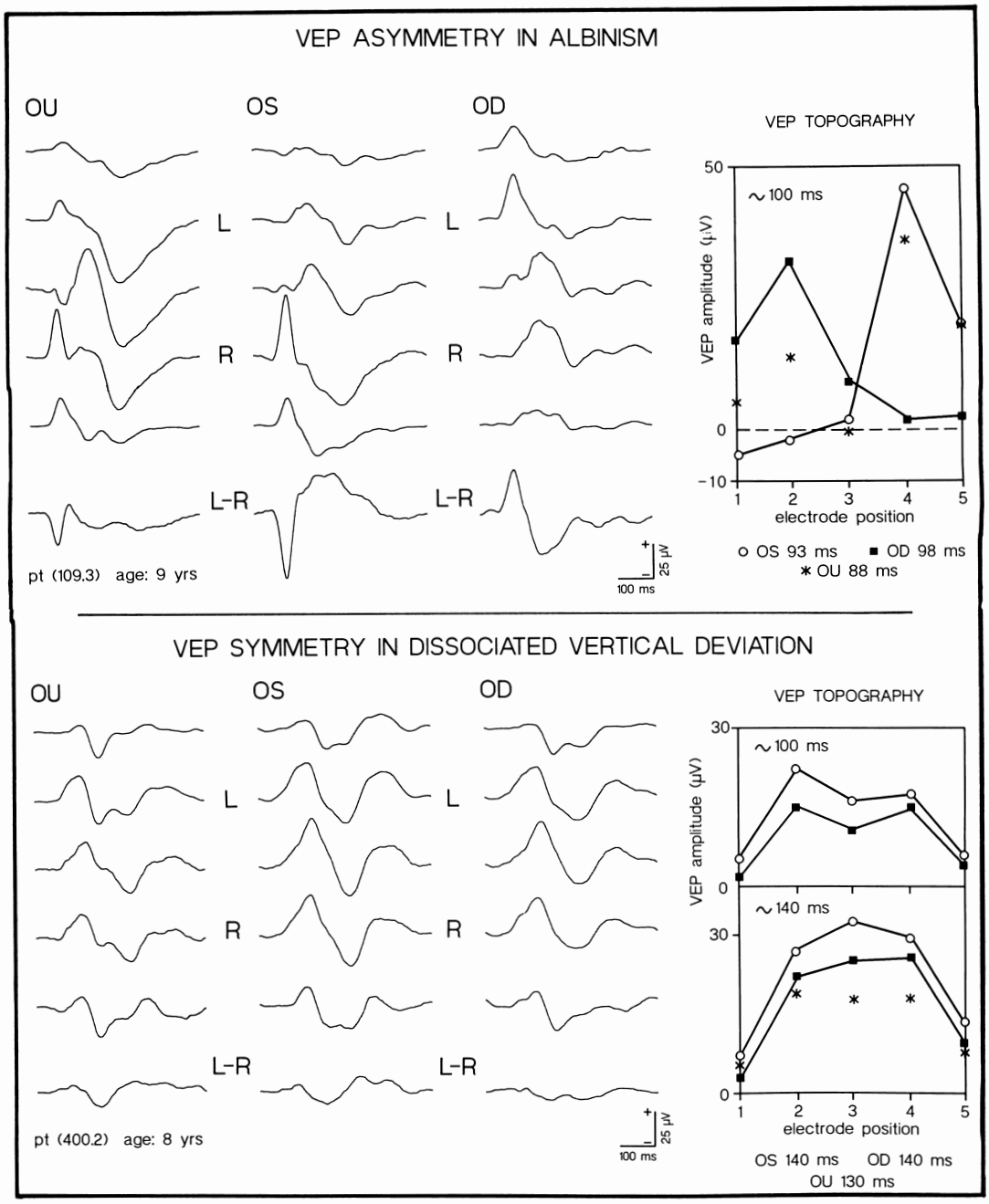
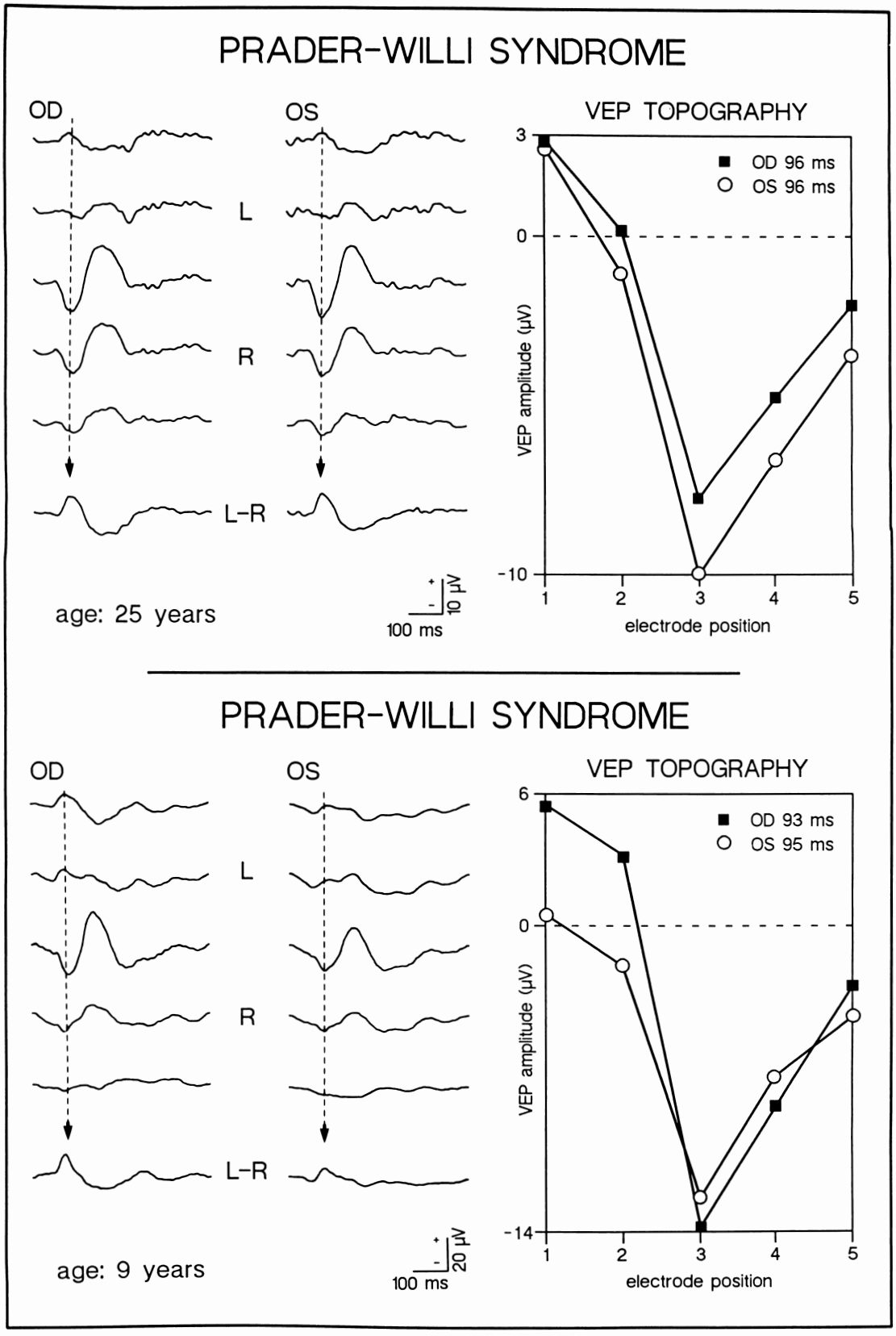


FIG 108–7.
Binocular *(OU),* left eye *(OS),* and right eye *(OD)* pattern-onset responses for an albino *(upper traces)* and an age-matched patient with DVD (*lower traces*). VEP amplitudes for *OU (starred symbols), OS (open circles),* and *OD (closed squares)* are plotted as a function of electrode position at the latencies specified. Note that, regardless of the latency window selected, the DVD patient shows no evidence of albino contralateral hemispheric asymmetry following full-field monocular stimulation.

FIG 108–8.
Left *(OS)* and right *(OD)* eye pattern-onset responses in two patients with Prader-Willi syndrome. The amplitude at about 100 ms (see the *dashed line*) is plotted as a function of electrode position. Both patients with Prader-Willi syndrome test negative for albino VEP asymmetry and instead present with a striking midline response attenuation. The monocular traces of both patients show a positive peak at about 100 ms that lateralizes to the left hemisphere. At the midline *(third trace from the top)* dramatic response negativity within the same latency window is present and followed by a later-latency positive peak. Within the age range depicted here (9 and 25 years), VEP albino asymmetry is reliably demonstrated within 80 to 110 ms after stimulus onset. In this example, despite a left hemispheric response dominance within this time period, the potential distribution



does not alter significantly from left to right eye stimulation. (From Apkarian P, Spekreijse H: The use of the electroretinogram and visual evoked potentials in ophthalmogenetics, in Desmedt JE (ed): *Visual Evoked Potentials*. Amsterdam, Elsevier Science Publishers, 1990, pp 169–223. Used by permission.)

which is not yet known, is rather remarkable. That previous authors report albino misrouting in this patient group can possibly be attributed to the curious and difficult-to-interpret Prader-Willi response profiles. On the other hand, it is possible that some patients with Prader-Willi syndrome who are purported to demonstrate misrouting may have indeed been albinos.

In conclusion, with appropriate stimulus and recording conditions as described in Chapter 54, the electrophysiological test of optic pathway misrouting is highly sensitive and selective. The VEP misrouting test is now indispensible for the detection and differential diagnosis of albinism.

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