

syndrome have had sons with lissencephaly and 1 of these mothers also has 2 daughters with double cortex syndrome [14]. These families lend support to the concept of an X-linked lissencephaly locus, with band heterotopia as a phenotype of manifesting female carriers with a mutation at this locus. We postulated that obligate female carriers in our family might show evidence of a partial migration disturbance on MRI but were unable to obtain consent for such studies. Epilepsy was not, however, seen in obligate carriers in our family.

To our knowledge, the family described in this report represents the first definite description of X-linked inheritance of agyria-pachygyria associated with agenesis of the corpus callosum. The possibility of a lissencephaly locus at Xq22 has been previously raised, based on the finding of a female with lissencephaly/agenesis of the corpus callosum and a balanced X:2 translocation. The findings in our family confirm a lissencephaly locus on the X chromosome, presumably a gene encoding a product required for neuronal migration. Molecular cloning of the Xq22 translocation break point and identification of gene(s) in this area may facilitate an understanding of the genetic basis for lissencephaly in our family as well as provide insight into mechanisms involved in neuronal migration.

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Syncope: A Videometric Analysis of 56 Episodes of Transient Cerebral Hypoxia

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To investigate the clinical features of transient cerebral hypoxia, syncope was induced in 56 of 59 healthy volunteers through a sequence of hyperventilation, orthostasis, and Valsalva maneuver. All events were monitored on video by two cameras. Complete syncope with falling and loss of consciousness was observed in 42 subjects, lasting 12.1 ± 4.4 seconds. Myoclonic activity occurred in 38 of these 42 episodes (90%). The predominant movement pattern consisted of multifocal arrhythmic jerks both in proximal and distal muscles. Superposition of generalized myoclonus was common. Additional movements such as head turns, oral automatisms, and righting movements occurred in 79%. Eyes remained open throughout syncope in most subjects and initial upward deviation was common. Sixty percent reported visual and auditory hallucinations. Thirteen subjects had incomplete syncope with falls but partially preserved consciousness. These episodes were shorter and usually not accompanied by myoclonus and hallucinations. Transient amnesia and unresponsiveness without falling occurred in 1 subject.

Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. *Ann Neurol* 1994;36:233-237

Syncope is commonly defined by loss of consciousness (LOC) and postural tone [1, 2]. Electroencephalographic (EEG) recordings of syncope typically show slowing, attenuation, and eventually cessation of cortical activity [3-5].

Additional clinical features of syncope include myoclonic jerks [5-8], eye movements [6], and hallucina-

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tions [7, 9]. To elucidate the clinical features of syncope in more detail we induced and monitored syncope in a series of healthy volunteers.

Subjects and Methods

Fifty-nine healthy students between 20 and 30 years of age (mean, 24 yr; 34 male, 25 female) volunteered for self-induction of syncope. Epilepsy, cardiac, and respiratory disorders were excluded by history, physical examination, and a resting electrocardiogram (EKG). The subjects were instructed not to drink alcohol for 24 hours, not to eat for 12 hours, and to sleep normally the night before testing.

After informed consent was obtained, subjects performed a sequence of 20 seconds of hyperventilation while squatting, fast rising to their feet, and finally a 10-second Valsalva maneuver with a forced expiration against the closed larynx. This procedure is known to lower cerebral perfusion rapidly by combining the effects of hypocarbic cerebral vasoconstriction, orthostasis, and a decreased venous return to the heart, which reduces cardiac output [10–12]. It is both effective and safe because all pathophysiologic factors end once the subject loses consciousness and reaches the horizontal [11, 12].

Falls were cushioned by a 2.5 × 3.5-m mat of foam rubber. The initial position was in a 30 × 30-cm recess of the mat to provide firm stance. For safety and to ensure proper video documentation subjects were prevented from falling forward by a helper. Otherwise the spontaneous sequence of events was not interfered with. Responsiveness was assessed by continuous request to count aloud.

All events were recorded by two high-resolution video cameras (Super-VHS), one covering the whole body, the other the eyes and face. A high-speed shutter of 1/250 second was used to avoid movement-induced blurring.

Each syncope was reviewed by two of us (T.L. and M.B.) approximately 100 times, both in real time and in slow motion. All episodes were evaluated with respect to responsiveness, falls, myoclonus, nonmyoclonic movements, eye movements, and vocalizations. Myoclonus was defined as an abrupt, brief, shocklike muscle activation. The individual experience of syncope was documented by a semistandardized interview that was conducted immediately after consciousness had returned.

The study was approved by the university clinic's medical ethics committee.

Results

Forty two of 59 subjects experienced complete syncope, which was defined as LOC and loss of postural balance. LOC was determined by both unresponsiveness and amnesia for the fall. Thirteen subjects fell without losing consciousness completely. These episodes were called incomplete syncope. LOC without falling occurred once. In the following we report the observations in the 42 subjects with complete syncope.

Duration of Syncope

Onset of syncope was marked by the incipient fall. Verbal responsiveness indicated its termination. Syn-

cope lasted 12.1 ± 4.4 seconds (range, 4.5–21.7 seconds). Nineteen subjects showed a partial response after 8.2 ± 4.0 seconds, which consisted of eye- and head-turning toward the assistant who gave the command to count.

Falls

Eighty-three percent of the subjects fell backward; the others tended to fall sideward or forward before they were directed backward. Forty-eight percent collapsed flaccidly with their knees flexed more than 90 degrees, while the remainder fell stiffly with their legs extended.

Myoclonus

Myoclonus occurred in 38 (90%) of 42 syncopal episodes. It never preceded the fall, starting 2.6 ± 0.9 seconds after LOC (range, 0.8–5.2 seconds) and lasting 6.6 ± 3.5 seconds (range, 0.7–15.9 seconds). It outlasted partial responsiveness in 10 subjects and verbal responsiveness in 4. These individuals usually remembered twitching when asked afterward. Myoclonic activity was mostly continuous with pauses never exceeding 1 second.

Myoclonus was classified as focal (only regional muscle activity throughout syncope), multifocal (widespread but asynchronous jerks), or generalized (widespread and synchronous muscle activation). Focal myoclonus occurred in 6 cases (16% of those with myoclonus) and exclusively generalized myoclonus in 1 (3%). Most common, however, was multifocal myoclonus (52%) and multifocal superimposed on generalized myoclonus (29%). Focal myoclonus lasted only 1 or 2 seconds, whereas multifocal myoclonus persisted for 8 seconds on the average, which makes the former appear as an abortive variant of the latter. This is confirmed by the rapid spread of seemingly focal myoclonus in those who eventually became multifocal.

Syncopal myoclonus was arrhythmic in all cases except 1. Most subjects showed both bilateral synchronous and asynchronous jerking. Synchronous muscle activity was either generalized or confined to the face, both arms, hands, legs, or feet. Proximal and distal muscles were equally involved. In a similar manner, there was no left or right predominance. Facial muscles were involved in 58%.

Other Movements

Motor activity other than myoclonus was observed in 33 syncopes (79%). Usually it started later than myoclonus; the mean onset was 4.7 seconds after LOC. Lateral head turns, sometimes accompanied by an ipsiversive gaze deviation, were quite common, but they never reached the forced tonic quality of epileptic head turns. Some subjects performed repetitive purposeless movements such as lip-licking, chewing, or fumbling, which resembled epileptic automatisms.

A righting movement was observed in 45%, con-

sisting of sustained head raising, sitting up, or even standing up while the subject was still unresponsive and amnesic. Mild extensor posturing occurred in 3 individuals. A lateral tongue bite was observed once in a subject with forceful multifocal myoclonus that involved masticatory muscles. Overt urinary incontinence did not occur.

Eye Movements

Eyes remained open during syncope in 76% of the subjects. Blinks were noted in one-half of the cases, mostly during reorientation. Sixty-six percent of those with open eyes had an initial upward deviation, sometimes accompanied by slight convergence; the others either remained in midposition or had a lateral deviation. In 50% the eye position changed subsequently, either returning into midposition or moving sideward. Transition from one position to another was slow, well below the speed of saccadic eye movements. Saccades usually reappeared some seconds before verbal responsiveness. In 1 case a primary position downbeat nystagmus was observed.

Vocalizations

Vocalizations occurred in 17 episodes (40%), on average starting 2.1 seconds after LOC with a mean duration of 2.7 seconds. Quite uniformly, they consisted of a continuous or intermittently accentuated moan of low pitch and voice.

Experience of Syncope

Visual and auditory hallucinations were reported by 60%. Subjects assigned them to the period of unconsciousness, but one-third described an overlap between fading hallucinations and return to consciousness.

All subjects with hallucinations reported visual phenomena. In some, they were restricted to perception of a gray haze, colored patches, or bright lights. Others experienced more realistic scenes that usually involved familiar places, situations, or persons. Four individuals described out-of-body experiences.

Auditory hallucinations were reported in 36%. They never appeared in isolation but accompanied visual delusions and ranged from rushing and roaring noises to screaming or talking human voices, but never contained intelligible speech.

Only 17% of the 42 subjects characterized the experience of syncope as a negative one, owing to the helplessness and disorientation, and 83% had a neutral or positive attitude. Commonly, subjects described a state of weightlessness, detachment, and peace, which some compared with previous drug or meditation experience.

Falling Without Loss of Consciousness

Thirteen subjects had incomplete syncope, which was characterized by at least partial preservation of con-

sciousness during the fall and thereafter. These individuals remembered their falls but were not immediately able to count aloud. They described a state of impaired external awareness, disorientation, and loss of voluntary motor control. These episodes were shorter (mean, 4.4 seconds) than complete syncope and usually not accompanied by myoclonus and hallucinations.

Loss of Consciousness Without Falling

The complementary type of dissociated syncope, that is, unresponsiveness without falling was observed once. This subject stumbled about after he had stopped straining, stared straight ahead, and was unable to count for 10 seconds. He needed another 30 seconds for full reorientation and was amnesic for the whole episode.

Electroencephalographic Recordings

Nine subjects who had succeeded in the self-induction of syncope were reexposed to the procedure on a separate occasion. This time, EEG was recorded during syncope with four electrodes in the C₃, C₄, P₃, and P₄ positions, and C_Z as a reference, as these locations had proved most resistant to head perturbation artifacts.

Six recordings reached sufficient quality for analysis. During hyperventilation and straining, the leads were superimposed by muscle activity. LOC coincided with high-amplitude theta and delta waves, which in 3 cases attenuated leaving a flat EEG. After a few seconds the same type of slow waves reappeared passing into alpha activity when consciousness returned. Myoclonic jerks occurred during the slow and the flat stages and were not accompanied by cortical discharges.

Discussion

In clinical practice physicians witness syncope with their own eyes only on rare occasions. Usually, diagnosis rests on a bystander's account so that many phenomena may go unnoticed or lead to an erroneous diagnosis of epilepsy [13, 14].

Myoclonus, which may be the most misleading symptom of syncope, has been recorded with various frequencies in previous studies, presumably depending on the precipitating mechanism and the accuracy of observation. Reported frequencies range from 12% in fainting blood donors [15] to 66% in syncope resulting from cardiac arrhythmia [5], 70% in acceleration-induced syncope [8], and 100% in syncope resulting from total arrest of cerebral circulation [6]. We observed syncopal myoclonus in 90%, suggesting that it represents rather the rule than the exception in the brain's response to hypoxia.

We found a typical pattern of syncopal myoclonus that consisted of both multifocal and generalized or other bilateral synchronous muscle activity. Individual differences concerned amplitude, frequency, and the mixture of multifocal and generalized myoclonus.

The origin of syncopal myoclonus has not been definitely established, but there is experimental and clinical evidence suggesting an activation of the medullary reticular formation. Microelectrode recordings from animals exposed to total brain ischemia showed preservation and even increase of medullary reticular activity for up to 40 seconds, whereas cerebral cortex potentials ceased after 10 to 12 seconds [16]. Different functional survival times are at least partially explained by the different oxygen demands of these brain regions [17].

Clinically, the stage of cortical suppression and medullary activation coincides with LOC and subsequent myoclonus. Like previous investigators we did not observe cortical discharges in the EEG during myoclonus but a sequence of high-amplitude slowing and flattening, which represents the typical EEG pattern of syncope [3–5].

The medullary reticular formation, specifically the nucleus reticularis gigantocellularis, is an established source of spontaneous and reflex myoclonus [18, 19]. Although reticular myoclonus is commonly described as generalized [20], we observed both generalized and multifocal muscle jerks in most subjects. A cortical origin of syncopal myoclonus, however, seems unlikely in view of the EEG findings. In a similar manner, a spinal generator is scarcely conceivable because spinal myoclonus is usually rhythmic, follows a segmental distribution, and does not spread to the face. Electrophysiologic studies are needed to further clarify the source of syncopal myoclonus.

The anatomical provenance of syncopal movements other than myoclonus remains uncertain. Among the various movement types a characteristic pattern deserves consideration; i.e., righting movements such as head raising, sitting up, or standing up occurred with remarkable frequency and consistency. Seemingly, they were not under voluntary control as they occurred in the midst of syncope when subjects were still amnesic and unresponsive. One might speculate that they represent a disinhibited labyrinthine righting reflex, thus indicating preserved function of the graviceptive otolith end organs and pathways [21].

Syncopal hallucinations are only occasionally mentioned in the literature [7–9, 22]. Vivid and pleasant illusions were reported by the majority of training airforce pilots who went through acceleration-induced LOC [8]. These have been related to more severe hypoxic episodes and have been allocated to the preorientation period [8, 9].

The experiences of patients who have been resuscitated from cardiac arrest, which implies a prolonged period of cerebral hypoxia, have received considerable public attention [23, 24]. These so called near-death experiences usually include a state of peace, the perception of bright lights, an unwillingness to return, and sometimes out-of-body experiences. Both patients and

authors tend to interpret these phenomena in transcendental terms [24, 25]. Their close resemblance to syncopal hallucinations, however, leads us to suggest hypoxic suppression of the neocortex and subsequent disinhibition of limbic structures as an alternative hypothesis.

Lesser degrees of hypoxia may induce incomplete syncope; some of our subjects were unable to remain upright while they felt dazed and disoriented but were still conscious. This dissociated state reflects the brain's regional vulnerability to hypoxia and is commonly referred to as near-syncope. The reverse phenomenon, which is unresponsiveness and amnesia with maintenance of upright stance, occurred once in our series and has not been reported before to our knowledge.

Postscript

A 7-minute videotape illustrating this study can be ordered at cost-price directly from the authors.

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Decreased Dopamine Transporters with Age in Healthy Human Subjects

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The effects of aging on brain dopamine transporters was evaluated in 26 healthy male volunteers (age range, 21–63 years) using positron emission tomography and [¹¹C]cocaine. The ratio of the distribution volume for [¹¹C]cocaine in basal ganglia to that in cerebellum was used as a model parameter for dopamine transporter availability and showed a significant negative correlation with age ($r = 0.65$, $p < 0.0005$). This results document an age-related decline in dopamine transporters in healthy individuals.

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It is generally agreed that there is a decline in brain dopamine (DA) activity with aging. Until recently most of the studies evaluating age effects on the DA system were performed in postmortem brains. However, the availability of new imaging techniques such as positron emission tomography (PET) and single-photon emis-

sion computed tomography (SPECT) enables us to measure neurotransmitter properties and therefore to evaluate these changes in living human subjects. In vivo studies overcome many of the problems of post-mortem studies such as medication use prior to death and cause and circumstances of death as well as factors affecting tissue preservation, all of which could affect DA measures.

Brain imaging has been used to investigate various elements pertaining to DA brain activity such as DA metabolism, D2 and D1 receptors, DA transporter sites, vesicular transporters, and monoamine oxidase (MAO) concentration. Studies on aging that have investigated changes in D2 and D1 receptors consistently showed a decrease in striatal D2 receptor density with aging [1–6] and a decline in D1 receptors in striatum and frontal cortex [7]. Studies on the effects of aging on the presynaptic DA terminals were less conclusive. Whereas decreases in DA transporters with aging have been documented [8], studies using ¹⁸F-fluorodopa to measure DA metabolism showed contradictory results, with one study reporting reduced uptake [9] and two others failing to show an age effect [10–11].

Several PET and SPECT ligands have been proposed as markers of the DA transporters (reviewed in [12]). The current study uses [¹¹C]cocaine and PET to evaluate the effects of normal human aging in the DA transporter. [¹¹C]Cocaine in the human brain binds predominantly to DA transporter sites [13] and [³H]cocaine has been shown to be sensitive to DA presynaptic degeneration in Parkinson's disease [14].

Materials and Methods

Twenty-six healthy male volunteers (age range, 21–63 years) who were screened for absence of medical, neurological, or psychiatric disease were selected for this study. Subjects in need of medication or with a history of alcohol or drug use (except for caffeine) were excluded. Prescan tests ensured absence of psychoactive drug use. Informed consent was obtained from the subjects following the guidelines of the Human Studies Review Committee at Brookhaven National Laboratory.

Scans were done using a whole-body, high-resolution PET instrument (6 × 6 × 6.5-mm full-width half-maximum at the center, 15 slices; Computer Technologies CTI 931). Positioning, preparation for the scans, and blood scanning protocol were done as previously described [13]. Dynamic emission scans were obtained after intravenous injection of [¹¹C]cocaine (4–11 mCi, 3–11 μg) [13]. Regions of interest in basal ganglia (BG) and cerebellum (CB) were obtained directly from the emission scans as described [13]. The time-activity curves for tissue concentration and for unchanged tracer in plasma were used to calculate the distribution volume for the BG and for the CB using a graphical analysis technique previously described [15]. The ratio of the distribution volume in the BG to that in the CB is insensitive to flow and is a measure of $(B_{max}/K_d)^{-1}$ [15]. This ratio was used as a measure of DA transporter availability. Correlation analyses were performed using Pearson product moment cor-

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